

# Diagnosis of Acute Appendicitis using Alvarado Score, Ultrasound Abdomen, and C-Reactive Protein in Different Combinations: A Prospective Observational Study

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## ABSTRACT

**Introduction:** Appendicitis is the most commonly encountered surgical emergency worldwide. Numerous diagnostic methods, including clinical scoring systems, radiological modalities, and laboratory markers have been suggested over time to diagnose appendicitis correctly, but a Negative Appendectomy Rate (NAR) of 20-30% is still maintained.

**Aim:** To determine the effect of using all three modalities together i.e., a clinical modality {The Alvarado Score}, a radiological modality {Ultrasound (US)}, and a laboratory parameter {C-Reactive Protein (CRP)} in diagnosing acute appendicitis.

**Materials and Methods:** This was a hospital-based, prospective observational study, carried out in the Department of General Surgery, SMS Medical College, Jaipur, Rajasthan, India, from March 2019 to June 2020. The three diagnostic modalities were arbitrarily categorised into different combinations: Combination 1: Alvarado score  $\geq 5$  with C-Reactive Protein (CRP)  $\geq 0.8$ ; Combination 2: Alvarado score  $\geq 5$  with US grade 4 with CRP  $\geq 0.8$ ; Combination 3: Alvarado score  $\geq 5$  with US grade 4 with CRP  $\geq 4$ ; and the individual modalities i.e., the alvarado score and the US abdomen were also categorised into four categories each. Each

of the individual modalities along with their different combinations were tested for their sensitivities, specificities, Positive and Negative Predictive Values (PPV, NPV) etc. Chi-square and t-test, sensitivity test and Receiver Operating Characteristic curve (ROC) and, Analysis of Variance (ANOVA) was used.

**Results:** Total 200 cases were analysed in this study with mean age  $32.33 \pm 15.78$  years. Alvarado score had a sensitivity and specificity of 95.83% and 75%, respectively. US had a sensitivity and specificity of 71.35% and 75%, respectively while CRP had the highest sensitivity with 98.96%, but very low specificity (37.5%). The sensitivity, specificity, PPV and NPV of the combination 1 were found to be 98.96, 37.50, 97.44, 60.00, and of combination 2 was found to be 70.83, 87.50, 99.27, 11.11 and for combination 3 was 56.77, 100, 100, 8.79, respectively. Combination 2 also had the highest Area Under Curve (AUC) in Receiver Operating Characteristic (ROC) curve.

**Conclusion:** The Combination 2 of three modalities proved to be the best diagnostic tool in the present study. It can pave the way, for a better diagnostic scoring system and future studies in this field.

**Keywords:** Appendicitis scoring systems, Diagnostic modalities, Negative appendectomy rates

## INTRODUCTION

The Appendix and its related diseases have been known to us ever since Berengarius Carpus described it in 1522 as an "additamentum" at the end of caecum [1]. Appendicitis is probably the most common cause of surgical acute abdomen and the first major surgery done by a surgical resident. The clinical picture of appendicitis has a broad spectrum, ranging from specific complaints like migratory right iliac fossa pain to non specific complaints like nausea, and vomiting [2]. Numerous diagnostic methods have been devised over time to diagnose appendicitis correctly, but a NAR of 20-30% is still maintained worldwide [2].

These include clinical scoring systems like the Alvarado Scoring System, Modified Alvarado scoring system [3], Raja IsteriPengiran Anak Saleha Appendicitis (RIPASA) Scoring System [2], Radiological modalities like US, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), laboratory markers like CRP, etc. The NAR has been shown to be as low as 5% with Contrast Enhanced Computed Tomography (CECT), but in a developing country like India, the cost of CECT abdomen increases the economic burden and does not seem to be a feasible option. It also possesses the disadvantage of increased exposure to ionising radiation [4,5]. Ultrasonography abdomen though, is highly operator dependent yet is a cheap and easily available diagnostic modality [4,6,7]. The same is true for total leucocyte count and CRP (an inflammatory marker).

The sensitivity and specificity of The Alvarado Scoring System and Modified Alvarado Scoring System have been shown to be 53-88% and 75-80% [2-4]. Studies done on Asian or Oriental populations have shown lower sensitivity of these scores as compared to the western population [8,9]. So, a scoring system incorporating all three diagnostic modalities i.e., clinical, radiological, and laboratory is actually needed to achieve a lesser NAR.

In the present study, the authors aimed to incorporate all three diagnostic modalities i.e., clinical modality (The Alvarado Score), radiological modality (US), and laboratory parameter CRP to have an accurate preoperative diagnosis and thus decrease the NAR. All these three modalities are easily accessible and economical and thus a proper diagnosis would help in decreasing the financial burden on the healthcare facilities and also the morbidity of a patient due to undue surgical stress.

## MATERIALS AND METHODS

This was a hospital-based, prospective observational study, carried out in the Department of General Surgery, SMS Medical College, Jaipur, Rajasthan, India, from March 2019 to June 2020. This study has been approved by the Institute's Ethical Committee (ethical committee no: 212/MC/EC/2020) and informed written consent was obtained.

**Sample size calculation:** By 95% confidence interval and 80% study power assuming a 71.3% prevalence of appendicitis confirmed

by biopsy results [10]. At a 10% allowable error of sample size, it was calculated that the study population should consist of at least 164 patients. After rounded-off and considering a 20% loss to follow-up, 200 clinically suspected acute appendicitis cases were included in the study.

**Inclusion criteria:** Adult patients aged 18-65 years of either sex, clinically suspected acute appendicitis (Alvarado score  $\geq 5$ ; score of 1-4 has been found to be too low for predicting appendicitis in previous literature) [11] and gave consent for investigations and treatment as per study protocols were included in the study.

**Exclusion criteria:** The patients whose physical examination notes were not sufficient for Alvarado scoring [2] or who do not have a CRP level on the same day, when they were medically examined or the ones who did not consented for the study and treatment and those operated on with appendectomy without histopathological evidence (gold standard for diagnosis) of acute appendicitis were excluded from the study.

### Study Procedure

The included patients were then subjected to different blood investigations including total leucocyte count, differential leukocyte count, CRP, and ultrasonography. Serum CRP was calculated on the day of presentation by blood assessment. The patient then underwent appendectomy and appendix was sent for histopathological examination. At follow-up, histopathology reports were collected and compared with preoperative investigations and Alvarado scores. Histopathological evidence of acute appendicitis was considered the gold standard for diagnosis. For establishing the authenticity of the above investigations individually and in combinations, the authors arbitrarily categorised these modalities into different combinations. The individual diagnostic modalities i.e., The Alvarado score and the US abdomen were also categorised into four categories [10]. Categories as per Alvarado score were:

- Group 1: score ( $\leq 4$ )
- Group 2: score (5,6)
- Group 3: score (7,8)
- Group 4: score (9,10).

As per US findings, the arbitrary categories were:

- Category 1: Normal appendix
- Category 2: Appendix not visualised, no secondary signs
- Category 3: Appendix not visualised, secondary signs present
- Category 4: Acute Appendicitis/Appendicular perforation [10].

The three arbitrarily made combinations of these three diagnostic modalities were as follows:

- Combination 1: Alvarado score  $\geq 5$  with CRP  $\geq 0.8$
- Combination 2: Alvarado score  $\geq 5$  with US grade 4 with CRP  $\geq 0.8$
- Combination 3: Alvarado score  $\geq 5$  with US grade 4 with CRP  $\geq 4$

### STATISTICAL ANALYSIS

Data was subjected to analysis using Statistical Package for the Social Sciences (SPSS 1.0.0.1406). ANOVA test was utilised for comparison between three or more groups. Chi-square test for comparing categorical data and for comparing the proportion of characteristics of interest between two samples. The t-test was used for continuous variables. Sensitivity, Specificity, PPV, and NPV was calculated using confusion matrix.

### RESULTS

Majority of patients included in the study belonged to the age group under 30 years [Table/Fig-1]. The mean age of presentation of cases was  $32.33 \pm 15.78$ . Out of 200 cases included, 192 had acute appendicitis in biopsy, 6 had normal appendix and 2 showed Meckel's diverticulum. NAR thus came to 4%.

Demographic characteristics	Count (%)
<b>Age (years)</b>	
Under 30	103 (51.5%)
31-50	67 (33.5%)
51-70	30 (15%)
<b>Sex</b>	
Male	97 (48.5%)
Female	103 (51.5%)

[Table/Fig-1]: Age and gender-wise distribution of patients.

Out of 8 cases that proved false positive for appendicitis after histopathology report, 6 were in Alvarado scoring category 2 while the other two were in category 3 (p-value 0.001). Moreover, out of these, 8 false positive cases, two belonged to US category 2, four were US category 3, and two were US category 4 (p-value-0.0002) [Table/Fig-2].

Description	Levels	Acute appendicitis	Not acute appendicitis	p-value
Groups/ Categories of Alvarado score	II	8 (4.16%)	6 (75.00%)	<b>0.001*</b>
	III	50 (26.04%)	2 (25.00%)	
	IV	134 (71.35%)	0	
	<b>Total (N)</b>	<b>192</b>	<b>8</b>	
Ultrasound categories	II	4 (2.08%)	2 (25.00%)	<b>0.002*</b>
	III	51 (26.56%)	4 (50.00%)	
	IV	137 (71.35%)	2 (25.00%)	
	<b>Total (N)</b>	<b>192</b>	<b>8</b>	
CRP level Mean $\pm$ SD		7.82 $\pm$ 6.76	2.65 $\pm$ 1.89	<b>0.0324#</b>

[Table/Fig-2]: Distribution of patients based on category of Alvarado score, Ultrasound (US) and C-Reactive Protein (CRP) levels.

\*Chi-square and #t-test was used

On comparing the three individual modalities, CRP had the highest sensitivity with 98.96%, but very low specificity (37.5%) making it high potential to increase NAR when used alone for diagnosis [Table/Fig-3].

Variables	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
CRP $\geq 0.8$	98.96	37.5	97.44	60	96.5
USG (Grade 4)	71.35	75	98.56	9.84	71.5
Alvarado score (Grade 3&4)	95.83	75	98.92	42.86	95
CRP $\geq 4$ v/s Perforated appendix	100	16.57	11.18	100	24.5

[Table/Fig-3]: ALVARADO Score, CRP and ultrasound, and their accuracies.

\*CRP: C-reactive protein; USG: Ultrasound; PPV: Positive predictive value; NPV: Negative predictive value

Combination 2 had good sensitivity and specificity and a comparable PPV. It also had the highest AUC in ROC curve. Although combination 3 had higher specificity and PPV than combination 2, a much weaker sensitivity made this combination inferior to combination 2 [Table/Fig-4].

Variables	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	AUC (95%)
Combination 1	98.96	37.5	97.44	60	96.5	0.682 (0.443-0.880)
Combination 2	70.83	87.5	99.27	11.11	71.5	0.792 (0.580-0.904)
Combination 3	56.77	100	100	8.79	58.5	0.784 (0.587-0.868)

[Table/Fig-4]: Accuracy of combinations.

AUC: Area under curve

The age-old Alvarado scoring system showed the highest AUC in the ROC curve owing to its higher sensitivity and good NPV. A higher sensitivity not only means a higher true positive but also higher false positives which in turn means a higher NAR [Table/Fig-5].

Area under the curve					
Test result variable(s)	Area	Standard error	Asymptotic significance <sup>b</sup>	Asymptotic 95% Confidence interval	
				Lower bound	Upper bound
Alvarado Score	0.901	0.037	<0.0001	0.830	0.973
CRP	0.872	0.048	<0.0001	0.778	0.967
USG	0.760	0.096	0.013	0.572	0.947
Combination 1	0.682	0.118	0.081	0.451	0.914
Combination 2	0.792	0.072	0.005	0.650	0.934
Combination 3	0.784	0.050	0.007	0.686	0.882

**[Table/Fig-5]:** Area under the curve for variables and combinations.

b: Significance calculated by logistics regression analysis

When Alvarado score was compared with CRP level, relationship between CRP levels and Alvarado score didn't show a significant relation (p-value- 0.0753) [Table/Fig-6].

Alvarado score category	CRP value (Mean±SD)
Category 2	5.23±6.75
Category 3	6.36±3.74
Category 4	8.35±7.47

**[Table/Fig-6]:** Relationship of Alvarado arbitrary categories and CRP values.

p-value- 0.0753 (not significant); ANOVA test was used

When US findings were compared with the CRP value, category 2 US patients had a mean CRP level of 4.62±2.69. This relation of CRP and appendicitis again was not significantly related. (p-value- 0.188) [Table/Fig-7].

Ultrasound category	CRP value (Mean±SD)
Category 2	4.62±2.69
Category 3	6.59±6.28
Category 4	8.15±6.94

**[Table/Fig-7]:** Relationship of Ultrasound (US) arbitrary categories and CRP values.

p-value- 0.188 (not significant); ANOVA test was used

## DISCUSSION

Early detection of acute appendicitis is very important to prevent multiple complications like an abdominal abscess, small bowel obstruction, and peritonitis. At the same time, an overzealous attitude towards appendectomy is also not fair and leads to a high NAR. NAR as per the present study (combining three diagnostic modalities) was 4% which is much below the rate found by another author i.e., 20-30% [2]. The reported sensitivity and specificity of Alvarado and modified Alvarado score range from 53-88% and 75-80%, respectively [12-15].

From the above results, it is evident that the Specificity of Alvarado score is not sufficient enough to decrease the NAR. It needs to be substantiated with another diagnostic modality to increase its specificity. In the present study, US grade 4 (appendix is visualised as inflamed or appendix is perforated) was used as the cut-off criteria for the diagnosis of appendicitis and it was found that it had the highest positive predictive value and specificity among the individual components. Two false positive cases were found to have Meckel's diverticulitis intraoperatively.

An approximate sensitivity of 83.75% and specificity of 95.94% have been found for US for diagnosing an equivocal acute appendicitis in a systemic review as well as a meta-analysis [16]. Similar sensitivities and specificities have been found by certain individual studies also.

Further NPV and PPV of US have also been calculated in various studies and a wide range is actually available (25-82% and 72-89%) [6,17,18].

The third diagnostic test was the CRP value. The CRP value cut-off was taken to be  $\geq 0.8$  as this was the value given in the study hospital laboratory as a baseline. A study has been conducted to calculate the sensitivity of biochemical markers and found out that CRP is the most sensitive perforation marker, but not accurate enough to be diagnostic [19]. In the present study also, the sensitivity of appendicular perforation with CRP was very high. But it had a very poor specificity suggesting that it alone cannot be used as a diagnostic tool. Thus, each of the individual modalities i.e., Alvarado score, US, and CRP have their own shortcomings and none of them is appropriate as a lone test to decrease NAR. So, combining these three modalities in different manners are needed to devise a better diagnostic scoring system which would ultimately help in decreasing the NAR [6,7].

The sensitivity, specificity, PPV, NPV, of the Combination 1 was found to be 98.96, 37.50, 97.44, and 60.00, respectively. Literature showed that Alvarado's score when combined with CRP improved the predictive value of diagnosing acute appendicitis [15]. In the present study also, the results were similar.

The sensitivity, specificity, PPV, and NPV of combination 2 was found to be 70.83, 87.50, 99.27, and 11.11, respectively. When all the parameters were combined, it improved the specificity and PPV value better than the individual components. Studies calculated that when the Alvarado score is combined with US, the specificity improved though compromising on its sensitivity [6,7,22]. When the three components are combined, literature shows sensitivity, specificity, PPV, and NPV of 51.9, 97.3, 97.9, 44.9, and 65, respectively [10]. Such studies, combining three diagnostic modalities have limited existence in previous literature thus adding significance to this study.

Such a combination with a very high CRP has not been studied much in previous studies and is probably unique to the present study. The authors also intend to initiate further studies to form a new scoring system incorporating all the above modalities and having the least NAR. Thus, Combination 2 of this study combining CRP, Alvarado Score, and US seems to be the best and most reliable to decrease the NAR.

## Limitation(s)

The present study has been conducted at a single centre, hence this conclusion needs to be studied and established in multicentre larger studies before generalising it to the population worldwide.

## CONCLUSION(S)

The three components under study (Alvarado score, US, and CRP) had a significant relationship with acute appendicitis. CRP was the most sensitive component among the three components. Combination 2 of the present study proved to be best for an accurate diagnosis of appendicitis with fairly good sensitivity and specificity. This combination can actually pave way for the development of a new scoring system involving all three diagnostic modalities i.e., Clinical (Alvarado score), Radiological (US), and Laboratory (CRP).

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