

## Evaluation of C-reactive protein in Combination with Alvarado Score System in Suspected Cases of Acute Appendicitis.

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**Abstract: Purpose:** To evaluate the sensitivity and specificity of C - reactive protein (CRP) in diagnosis of acute appendicitis for suspected cases and possibility of adding it to Alvarado scoring system. **Materials and Methods:** This is a cross sectional prospective study of 124 patients who underwent appendectomy because of suspected acute appendicitis. Alvarado score was determined and considered significant when it is  $\geq 7$ . CRP level was reported and considered abnormal when its level is above 12 mg/dl. Combination of both was labelled as combined integrated test. If both were abnormal, the test was considered positive. Patients were categorized into 3 groups based on histopathological findings: normal appendix, acute appendicitis or complicated appendicitis. **Results:** Normal appendix was found in 24 patients (19.4%), acute appendicitis in 79 (63.7%) and complicated appendicitis in 21 (16.9%). Alvarado score was  $\geq 7$  in 66 (83.5%) of acute appendicitis patients and in all 21 (16.9%) of complicated appendicitis patients. CRP level was high in 98 (79%) with mean of 62.3 mg/dl in 66 (83.5%) of acute appendicitis patients and 129.1 mg/dl in 19 (91%) of complicated appendicitis patients. Positive combined integrated test was found in 85 (68.5%) and 78 (92%) had appendicitis. Combined integrated test showed sensitivity of 78% and specificity of 71%. **Conclusion:** Combining CRP level with Alvarado score system showed sensitivity of 78% and specificity of 71%. Although that diagnosis of acute appendicitis usually based on clinical judgment, combined integrated test can be used to improve the accuracy of diagnosis and reduce the number of negative appendectomies. It is simple, cheap and can be obtained immediately to establish diagnosis.

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### 1- Introduction

Acute appendicitis is the most common surgical emergency with prevalence of 8% and incidence rate of 1.5- 1.9 /1000 of population<sup>(1,2)</sup>. Clinical presentation of acute appendicitis is mainly based on periumbilical migratory pain to the right iliac fossa as described by **Murphy in 1904**. The full picture of acute appendicitis can be recognized only in 50% of cases. The remaining attributes a continuing challenge specially at the extreme of age and females in child bearing period which needs a high index of clinical skills strengthened by laboratory and imaging studies. Nausea, vomiting, anorexia as well as low grade fever are associated with that entire pain. Clinical picture may be subtle to clinician and patient when not presented in all cases<sup>(3)</sup>. Careful history and clinical examination, total leukocytic count remained the gold standard in diagnosis of acute appendicitis<sup>(4)</sup>.

Alvarado Score gathered clinical manifestation with simple blood tests as a tool in diagnosis of acute appendicitis to reduce the number of negative appendectomy. Alvarado developed that score based on a cohort study at Nazareth Hospital in Philadelphia in 1986<sup>(5,6)</sup>. The variables of the score

fall under the mnemonic. MANTRELS which displays Migratory pain to the right iliac fossa, Anorexia, Nausea or vomiting, Tenderness, Rebound tenderness, Elevated body temperature  $> 37^{\circ}.3$  C, Leukocytic count  $> 10,000$ , Left Shift or neutrophilia. Each variable scores one point except tenderness and leukocytosis which score 2 points each. That makes the total score of 10. In 1994, **Kalan et al** stated that the score is subjected to modification via omitting neutrophilia to make its final limit 9 points

C - reactive protein (CRP) is an acute phase protein which rises in various inflammatory conditions. It reacts as precipitin with the C-Polysaccharide of pneumococci and enhances cell-mediated immunity<sup>(7)</sup>. When CRP is added to the laboratory investigation, it may improve the accuracy of diagnosis of acute appendicitis and reduce the relatively high incidence of negative appendectomy. This study was designed to evaluate the sensitivity and specificity of CRP in diagnosis of acute appendicitis for suspected cases and possibility of adding it to Alvarado scoring system.

## 2. Materials and Methods

This is a cross sectional prospective study of 124 patients who were admitted and underwent appendectomy at King Abdulaziz University Hospital (KAUH) between September 2011 and September 2012 because of suspected acute appendicitis. After taking ethical approval from the local ethical committee, detailed case history was taken, clinical examination and laboratory blood test for leukocytic count, neutrophilic count and CRP level were done, and Alvarado score was determined and categorized into 3 classes (A score < 5, A score = 5-6 or A score  $\geq$  7) for each patient.

CRP was estimated by quantitative method using Behring nephrometry. CRP level was reported and considered abnormal when its level is above 12 mg/dl and special consideration was taken when CRP level is above 100 mg/dl. Alvarado score considered significant when it is  $\geq$  7. Combination of Alvarado score and CRP was labelled as combined integrated test. When both Alvarado score is significant and CRP level is abnormal, the combined integrated test considered positive.

Surgical management was decided for the patients based on clinical impression only. Some cases were subjected to imaging studies e.g. abdominal X-ray, ultrasound or C.T scan but findings were ranked as exclusion data. Patients were categorized into 3 groups based on histopathological findings of resected appendix into normal appendix, acute appendicitis or complicated appendicitis (gangrenous or perforated).

The data were entered and analyzed using the statistical package for social sciences (SPSS Inc, Chicago, IL, USA), version 16.00.

## 3. Results

Total of 124 patients were included, 69 were males (55.6%) and 55 were female (44.4%) with mean age of 24.4 years (range 11-36 years).

Normal appendix was found in 24 patients (19.4%), acute appendicitis in 79 (63.7%) and

complicated appendicitis in 21 (16.9%). Alvarado score was applied to all patients who underwent appendectomy. Only 6 patients (4.8%) scored < 5, 17 (13.7%) had score 5 - 6 and 101 (81.5%) scored  $\geq$  7. Table-1 shows Alvarado score in patients with normal appendix and appendicitis.

High Alvarado score (A score  $\geq$  7) was found in 14 (58.3%) of normal appendix, 66 (83.5%) of acute appendicitis and in all 21 (100%) of complicated appendicitis. Alvarado score 5-6 was found in 5 (20.8%) of normal appendix, 12 (15.2%) of acute appendicitis and none of complicated appendicitis. Low Alvarado score (A score < 5) was found in 5 (20.8%) of normal appendix, 1 (1.3%) of acute appendicitis and none of complicated appendicitis. (This is may be used as good -ve test).

The high score  $\geq$  7 had prevalence in our study 101 out of 124 (81.4%), among them only 14 out of 101 (13.8%) had normal appendix, 66 (65.3%) had acute appendicitis and 21 (20.7%) had complicated appendicitis. This made sensitivity of 83% and specificity of 46 % for Alvarado Score System.

Regarding CRP, only 26 out of 124 (21%) were considered normal while 98 (79%) showed high levels of CRP with mean of 62.3 mg/dl in 66 (83.5%) of acute appendicitis patients and 129.1 mg/dl in 19 (91%) of complicated appendicitis patients. CRP level  $\geq$  100 mg/dl was noticed in 40 patients and 36 (90%) of them confirmed acute or complicated appendicitis. Table-2 showed CRP level in patients with normal appendix and appendicitis.

Combined integrated test was positive in 85 (68.5%) of patients and negative in 39 (31.5%). Seventeen (70.8%) of normal appendix had -ve combined test and 78 (92%) of acute and complicated appendicitis displayed +ve combined test. That results in sensitivity of 78% and specificity of 71% for the combined integrated test. Table-3 shows combined integrated test in patients with normal appendix and appendicitis.

**Table-1: Alvarado score in patients with normal appendix and appendicitis before appendectomy**

	A Score < 5 (n) %	A Score 5-6 (n) %	A Score $\geq$ 7 (n) %	Total (n)	Percentage %
Normal Appendix	5	5	14	24	19.4%
Acute Appendicitis	1	12	66	79	63.7%
Complicated Appendicitis	0	0	21	21	16.9%
<b>Total</b>	<b>6 4.8%</b>	<b>17 13.7%</b>	<b>101 81.5%</b>	<b>124</b>	<b>100%</b>

**Table-2: CRP level in patients with normal appendix and appendicitis**

	-ve CRP < 12mg/dl n (%)	+ ve CRP $\geq$ 12mg/dl n (%)	Total	Mean CRP (mg/dl)
Normal Appendix	11 (46%)	13 (54 %)	24	36.1
Acute Appendicitis	13 (16.5%)	66 (83.5%)	79	62.3
Complicated Appendicitis	2 (9%)	19 (91%)	21	129.1
<b>Total</b>	<b>26</b>	<b>98</b>	<b>124</b>	

**Table-3: Combined integrated test in normal appendix and appendicitis**

	+ve Combined integrated test n (%)	-ve Combined integrated test n (%)	Total
Normal Appendix	7 (8%)	17 (44%)	24
Acute and Complicated Appendicitis	78 (92%)	22 (56%)	100
Total	85 (100%)	39 (100%)	124

**Table 4: Number of Appendectomies with CRP > 100 mg/dl**

	Number of Appendectomies with CRP > 100 mg/dl	Percentage (%)
Normal Appendix	4/24	16.7
Acute Appendicitis	21/79	26.9
Complicated Appendicitis	15/21	71.4
Total	40/124 (32.2% of all appendectomies)	

**Table-5: Comparison between the 3 Indices used in our study**

	Alvarado Score	CRP	Combined Parameters
Sensitivity	0.85	0.83	0.78
Specificity	0.46	0.46	0.71
Prevalence	0.81	0.81	0.81
Positive Predictive Value	0.87	0.87	0.92
Negative Predictive Value	0.46	0.38	0.44
Positive Likelihood	1.57	1.54	2.67
Negative Likelihood	0.33	0.37	0.31
Overall Accuracy	0.77	0.76	0.77

**Table-6: Management plan of suspected appendicitis**

	Score <5	Score 5-6	Score ≥7
Normal CRP	Home	observe	Image
High CRP	Observe	Image	Operation

#### 4. Discussion

Acute appendicitis is a common surgical emergency which has 50% ratio of atypical presentation that contributes a real challenge in diagnosis which necessitates clinical skills augmented by simple blood tests. Negative appendectomy was found 18.6% in our study which may be due to the role of imaging studies. In literatures, negative appendectomy ranges between 15%-30%<sup>(8)</sup>. One study showed 50% negative appendectomies in female in the reproductive period. That was significantly high percentage can be justified to avoid complications of neglected appendicitis, the concept of "When you are in doubt Take it out" still valid between surgeons.

That incidence was a bit higher in females in our study. It constituted 53.8% (14/26) of all negative appendectomies. We planned our study to evaluate the efficacy of Alvarado score when coupled with one of the important inflammatory marker, CRP in diagnosis of acute appendicitis tempting to reduce the number of negative appendectomies. All patients with right iliac fossa pain showed in the emergency department in our hospital were clinically assessed in addition to some simple laboratory tests as WBC count, Neutrophil count as far as C-reactive protein.

**Olakolu et al (2011)**, studied 53 patients for Alvarado score, his work showed sensitivity, specificity and accuracy 82.4%, 52.6%, 72% respectively<sup>(5)</sup> compared to 83%, 46% and 76% in our study.

CRP is an acute phase protein which is released in response to inflammatory conditions, it enhances cell-mediated immunity by promoting phagocytosis, accelerating chemo taxis and activate platelets. CRP can be also used in screening the organic diseases and monitoring the response of treatment. The mean value of CRP in our study of normal appendix, acute and complicated appendicitis was 36.1 mg/dl, 62.3mg/dl and 129.1mg/dl respectively. Through these results we can figure that CRP corresponds to the severity of the disease. Our mean values of CRP were higher than those mentioned by **Gurleyik et al (1995)** which were 5 mg/dl, 33.8 mg/dl, 128.5 mg/dl for the corresponding groups respectively<sup>8</sup>. **Birchley 2006** suggested that higher level of CRP refers to complicated appendix as abscess. High CRP value may predict severity of acute appendicitis<sup>(9,10)</sup>. Another novel finding in our study in term of CRP results is the very high finding > 100 mg/dl in 40 cases 40/124 (32.2%) which ranged from 100 mg/dl up to 348 mg/dl. 36 out of 40 cases (90%) of these cases of ≥100 mg/dl CRP showed pathological appendix (Table-4).

Only 4 cases of normal appendix (16.7%) had that high CRP value, while 21/79 of the acute

appendicitis (26.9%), most of the complicated cases 15/21 (71.4%) with very high CRP value which may correlated to the severity of the disease.

Raised values of CRP were directly related to the severity of inflammation and enhance the diagnostic accuracy of acute appendicitis<sup>(11,12,13)</sup> while normal CRP is most likely associated with normal appendix<sup>(14)</sup>. CRP is included in the diagnostic decision making protocol in Finland<sup>(15)</sup>.

On the other hand, some authors did not support the idea of using CRP as a sole index to diagnose or predict acute appendicitis<sup>(16,17,18)</sup>. While others accepted CRP when incorporated with other indices as WBC and other inflammatory variables<sup>(19,20,21,22,23)</sup>.

In our study we combined Alvarado score system with CRP that improved specificity. The integrated test of Alvarado score with CRP as a sole tool of diagnosis of acute appendicitis as applied in our study.

Specificity was markedly improved to 71% while sensitivity kept less than the individual marker sensitivity that may be due to strict criteria of positivity i.e. Only one condition was considered positive when Alvarado score and CRP were simultaneously high, otherwise was considered negative. The overall accuracy remained nearly the same.

**Shafi et al,2011**<sup>(3)</sup> and **Eriksson et al 1994**<sup>(24)</sup> concluded that negative appendectomy had been fallen from 24% to 16 % when CRP and Alvarado or modified Alvarado score (MAS) were preoperatively applied, **Shakhatreh (2000)** looked at CRP as a helpful diagnostic tool from acute appendicitis without replacing the clinical skills<sup>(25)</sup>.

The advantages of CRP as a less expensive, objective, readily available with no risk of irradiation were mentioned by **Ohle et al, 2011** through their fantastic review<sup>(26)</sup>. On the other hand, Alvarado score has the privilege of not excluding clinical evaluation. Coupling of these tools supports the sound clinical decision.

We do advice discharge for patients with low Alvarado score and normal CRP, while operation is mandated to patients with high score and high CRP, giving attention to the very high values which refer to severity. Patients in the grey zone between these latter groups are good candidates for observation and imaging studies (Table-6).

## Conclusion

Combining CRP level with Alvarado score system showed sensitivity of 78% and specificity of 71%. Although that diagnosis of acute appendicitis usually based on clinical judgment, combined integrated test can be used to improve the accuracy of

diagnosis and reduce the number of negative appendectomies. It is simple, cheap, reliable, does not need sophisticated equipment or technical expertise and can be obtained immediately to establish diagnosis.

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