

THE ADVANTAGE OF ACUTE INFLAMMATORY MARKERS IN DIAGNOSIS OF ACUTE APPENDICITIS

Mazin H Al-Hawaz*, Mazin A Abdulla[@] & Hyder Dakhel Ali[#]

*MB,ChB, CABS, DGS, FRCS, Professor of General Surgery, Dean of Al-Zahraa College of Medicine, Head of Department of Surgery, Basrah College of Medicine, Basrah, IRAQ. [@]MB,ChB, CABS, Assist. Prof. of General Surgery, Dept. of Surgery, Basrah Medical College. [#]MB,ChB, Iraqi Board Candidate.

Abstract

Acute appendicitis is the most common cause of emergency abdominal surgery with an estimated lifetime prevalence of 7%–8%. Despite advances in diagnosis and treatment, it is still associated with morbidity (10%) and mortality (1%–5%).

This study was designed to investigate the results of WBC count, platelet distribution width and C-reactive protein values based on the pathology results in patients undergoing appendectomy with an early diagnosis of acute appendicitis.

This prospective cross sectional study was carried out in Basrah Teaching Hospital from the period 1st of September 2015 to 1st of June 2017, a total of 154 consecutive patients were enrolled in the study. All patients were admitted to the emergency department with history suggestive of acute appendicitis, blood tests were done for inflammatory markers in form of WBC, CRP and PDW, a period of 24 hours prior to surgery was accepted, histopathological data were used to assess inflammation of the appendix.

The majority of patients were males 61% while females were 39%, with age range between 14-46 years (mean 24.28 years). There was a correlation between WBC count and acute appendicitis (P value=0.004), with sensitivity range (53%-69%) and specificity range (25-89%), while positive predictive value (PPV) and negative predictive value (NPV) were 96% and 8% respectively. A significant correlation found between CRP and acute appendicitis (p value less than 0.0001) with sensitivity range (71%-85%), while specificity was (10%-74%) and PPV, NPV were 95% and 9% respectively. Regarding PDW, no correlation was found with acute appendicitis (p value=0.296) with sensitivity range (6%-16%) while specificity (17%-82%), PPV 78%, NPV 2%. There was significant correlation between inflammatory markers (WBC, CRP, PDW) and complication with a p value=0.0001, ruptured appendix and peri-appendicular abscess were the most common complications recorded, only 8(5.2%) patients had normal appendix after histopathological examination.

In conclusion, acute inflammatory markers play an important role in diagnosis of acute appendicitis along with history and physical examination.

Introduction

Acute appendicitis is the most common cause of emergency abdominal surgery¹ with an estimated lifetime prevalence of (7%–8%). Despite advances in diagnosis and treatment of this condition, it's still associated with morbidity (10%) and mortality (1%–5%)². Laboratory blood tests form part of pre-operative diagnostic work-up for suspected acute appendicitis and feature in some clinical scoring systems for appendicitis³.

Current biomarkers attempt to identify the presence of inflammation together

with a suggestive history and examination may help to make informed decision to perform imaging or surgery in those with suspected appendicitis⁴.

The most commonly used laboratory tests in the diagnosis of acute appendicitis are leukocyte count, C-reactive protein (CRP)⁵ and neutrophil count (absolute value or percentage of WCC)⁶.

In general, patients have a moderately increased number of leukocytes (10,000/mm³) with a prevalence of neutrophils. Leukocytes above 20,000/mm³ usually indicate

complications as diffuse peritonitis⁷. Narci found cutoff value of WBC $10.4 \times 10^3/\text{mm}^3$ with a 91% sensitivity and 74% specificity⁸.

Recent studies showed that the sensitivity of neutrophil leukocyte ratio (which has been shown as a good inflammatory changes marker) was 60.1% and specificity 76.9% in diagnosing acute appendicitis⁹.

C-reactive protein levels are related to the evolution of the infection of the appendix, and values above 50 mg/dl indicate necrosis and perforation of the appendix. The specificity is usually higher combined with the leukocyte count, amounting to about 38-87%, and its sensitivity up to 94%¹⁰.

White Blood Cells and CRP remain the most used laboratory findings for distinguishing patients with appendicitis from those without. Studies showed that WBC seems to be a very early marker of appendiceal inflammation¹¹.

Serum inflammatory markers seem to be age-dependent in acute appendicitis, normal WBC count and CRP in adults exclude diagnosis of acute appendicitis with a predictive value 100%, while in children aged less than 13 years normal values does not effectively exclude the diagnosis with a percentage of 7% of histologically proven acute appendicitis with normal counts¹².

Platelet distribution width (PDW) are presented in the complete blood cell count, studies showed that it is higher in perforated appendix⁷. This study aimed to evaluate the results of WBC count, CRP and PDW based on the pathology results in patients undergoing appendectomy, whether inflammatory markers aids in diagnosis and prevention of further complication due to delay in diagnosis.

Patients and Methods

This a prospective cross sectional study carried out in Basrah Teaching Hospital between 1st of September 2015 to 1st of June 2017 and it included 154 consecutive

patients (94 males 60 females) who underwent appendectomy. Baseline demographic data were recorded for each patient as age, gender, and date of operation.

Full detailed history was taken for all patients and followed by complete physical examination for signs of acute appendicitis.

Blood tests were done for inflammatory markers in form of WBC, C-reactive protein and platelet distribution width (PDW).

All blood tests were performed on blood samples obtained via venous system and collecting into EDTA tubes and analyzed by cobra integra 400 plus regarding CRP while CBC analysis by sysmex xt 2000i.

The upper limits of the reference ranges were as follows: Leukocyte counts (WBC) $4500-11000 \times 10^6/\mu\text{L}$, Platelet: $130-400 \times 10^3/\mu\text{L}$, Neutrophil: $2-6.9 \times 10^3/\mu\text{L}$ (37%-80%), Lymphocyte: $0.6-3.4 \times 10^3/\mu\text{L}$ (10%-50%), MPV: 7.2-11 fL, RDW: 11%-16%, PDW: 5%-15% and CRP: 0-5 mg/dl. Values categorized as WBC (more than $11000 \times 10^6/\mu\text{L}$ as high, higher than $15000 \times 10^6/\mu\text{L}$), PDW (more than 15% as high), CRP (more than 5% as high and higher than 15%).

Based on histopathological data, acute appendicitis was categorized into: None complicated and complicated: (Ruptured appendix, perforated appendix with subsequent peritonitis, gangrenous appendix, peri-appendicular abscess, adhesion). Presence of other pathologies related to female genital tract was also recorded if present.

All data were collected and analyzed by using SPSS analyzer system 15.1 and a P value less than 0.05 was considered to be significant.

Results

A total of 154 patients underwent appendectomy, the majority of patients were males 94(61%) while females were 60(39%) with total mean age of 24.28, the mean value of WBC in males was higher

($15111 \times 10^6/\mu\text{L}$) than in females ($13476.6 \times 10^6/\mu\text{L}$), total mean value of WBC was $14474 \times 10^6/\mu\text{L}$ which is above of normal value, PDW was higher in males with mean value (10.9%) than in females (10.67%). Regarding C-reactive protein, the mean value in females was higher than that in males (Table I).

Table I: Demographic data and inflammatory markers.

Gender		Age	WBC($\times 10^6/\mu\text{L}$)	PDW (%)	CRP (mg/dl)
Males (94)	Mean	23.85	15111.7	10.9	13.5
	S.D	9.19	16454.3	3.32	11.79
Females (60)	Mean	24.9	13476.6	10.67	14.14
	S.D	8.34	13545.02	3.35	11.95
Total (154)	Mean	24.28	14474.6	10.8	13.75
	S.D	8.85	15360.9	3.33	11.8

Sixty one (39.6%) patients presented with normal range of WBC, the remaining 93 (60.4%) patients had values of $11.000 \times 10^6/\mu\text{L}$ and above, C-reactive protein was elevated in 121 (78.6%). Regarding platelet distribution width, the majority of patients 133 (86.4%) had normal value, 2 patients had low PDW and 19 patients had more than 15% PDW (Table II).

Table II: Values of inflammatory markers in this study

Inflammatory markers	Frequency	Percentage
White blood cells $\times 10^6/\mu\text{L}$		
4.000-11.000	61	39.6%
more than 11.000	57	37.0%
higher than 15.000	36	23.4%
C-Reactive protein mg/dl		
Less than 5	33	21.4%
More than 5	74	48.1%
Higher than 15	47	30.5%
Platelet distribution width %		
Less than 5	2	1.3%
5-15	133	86.4%
More than 15	19	12.3%
Total	154	100%

Histopathological examination proved presence of appendicitis in 146 patients with catarrhal type in 79 (51.3%) patients, severely inflamed appendix in 50 (32.5%) patients while fecalith appendicitis and tumor noticed in (9.7% and 1.3%) of patients, respectively. Only 8 patients (5.2%) had normal appendix in the pathological data. Regarding status of inflammatory markers concomitant with different histopathological types seen in our patients, WBC was elevated with mean value of $14.5 \times 10^6/\mu\text{L}$ in catarrhal appendicitis found in 79 (51.3%) patients and it was higher at $16.8 \times 10^6/\mu\text{L}$ in 50 (32.5%) patients with severely inflamed appendix. In normal appendix (8 patients), fecalith type (15 patients) and tumor (2 patients), WBC was nearly within normal range (Table III).

Table III: Correlation between inflammatory markers (WBC, CRP, PDW) and histopathological data for patients with suspected appendicitis.

Inflammatory markers		Histopathological finding						P value
		Normal appendix	Catarrhal appendicitis	Severely inflamed appendix	Fecalith appendicitis	tumor	Total	
WBC $\times 10^6/\mu\text{L}$	4.000-11.000	7	31	13	9	1	61	0.004
	11.000-15.000	0	35	17	4	1	57	
	More than 15.000	1	13	20	3	0	36	
Total		8	79	50	15	2	154	
CRP Mg/dl	Less than 5	3	19	5	6	0	33	<0.0001
	5-15	4	47	19	5	0	74	
	More than 15	1	13	26	5	2	47	
Total		8	79	50	15	2	154	
PDW %	Less than 5	0	2	0	0	0	2	0.296
	5-15	8	70	40	14	1	133	
	More than 15	0	7	10	1	1	19	
Total		8	79	50	15	2	154	

Estimation of C-reactive protein according to histopathological examination was: 11 mg/dl in patients with catarrhal appendicitis, 18.5 mg/dl in patients with severely inflamed appendix with or without abscess formation, 15 mg/dl in patients with fecalith appendicitis and 29 mg/dl in patients with tumors (Table III). While PDW was mildly elevated in catarrhal appendicitis and severely inflamed appendix with abscess formation. In tumor of the appendix, the mean value of PDW was 14 %. There was correlation between WBC values and pathological data. Most of the patients had WBC values between (11.000-15.000), with WBC values more than $15.000 \times 10^6/\mu\text{L}$ was mainly found in severely inflamed patient (20 out of 36 patients (Table III). Regarding CRP, there was significant correlation (p value < 0.0001) with pathological data as most of patients had high values (>5 mg/dl), particularly those with catarrhal appendicitis, while those with severely inflamed appendix had CRP more than 15 mg/dl which also found in those with tumors. No correlation was found between PDW and pathological

data (p value=0.296) with majority of patients had values within the normal range 5-15 % and only 19 out of 154 had values higher than 15 distributed between catarrhal appendicitis (7), severely inflamed appendix (10), one fecalith and one patient with tumor (Table III). Most of patients had no complications (81.8%) followed by ruptured appendix in (5.8%), peri-appendicular abscess (5.2%) and perforation with subsequent peritonitis (4.5%). Gangrenous appendix and adhesion was seen in 4 patients only representing 1.3% for each. One hundred twenty six patients out of 154 study patients had no complication with 71 of patients had WBC more than $11.000 \times 10^6/\mu\text{L}$, either severely inflamed appendix or those with ruptured ovarian cyst. Those with complications had WBC more than $15.000 \times 10^6/\mu\text{L}$. This indicates that complication correlates positively with elevated WBC values (Table IV). Complications of acute appendicitis correlates significantly with elevated values of CRP as in patients with perforation and subsequent peritonitis, gangrenous appendicitis, and adhesion who had values more than 15 mg/dl.

While those with ruptured appendix and peri-appendicular abscess had moderate to highly elevated CRP (Table IV).

Regarding PDW, those with perforation and subsequent peritonitis, gangrenous and peri-appendicular abscess had highly elevated values (more than 15%), patients

with ruptured appendix and adhesions had values between moderate to elevated PDW, which indicates a significant correlation between PDW and complication of acute appendicitis as demonstrated in Table IV.

Table IV: Correlation between inflammatory markers and complications of appendicitis

Inflamm. markers		Complications						Total	P value
		None	Ruptured appendix	Perforation with subsequent peritonitis	Gangrenous appendix	Peri – appendicular abscess	Adhesion		
WBC	4.000-11.000	55	2	0	0	3	1	61	0.004
	More than 11.000	52	4	0	0	1	0	57	
	Higher than 15.000	19	3	7	2	4	1	36	
	Total	126	9	7	2	8	2	154	
CRP	Less than 5	31	1	0	0	1	0	33	<0.0001
	More than 5	69	2	0	0	3	0	74	
	Higher than 15	26	6	7	2	4	2	47	
	Total	126	9	7	2	8	2	154	
PDW	Less than 5	2	0	0	0	3	0	5	0.296
	5-15	121	6	1	1	1	0	130	
	More than 15	3	3	6	1	4	2	19	
	Total	126	9	7	2	8	2	154	

Discussion

Acute appendicitis is sometimes difficult to diagnose despite its classical signs and symptoms being well known^{13,14}. In addition delay in diagnosis is associated with perforation and increased complication rate¹⁵.

In this study we planned to investigate the value of inflammatory markers in the diagnosis of acute appendicitis, although some studies showed no superiority of inflammatory markers to accurate history, physical examination and laboratory studies in diagnosing acute appendicitis¹⁶. Many studies support that WBC is the first indicator to be elevated in AA, in this study there was a significant correlation between WBC count and acute appendicitis (P value = 0.004) with

sensitivity 61% and Specificity 62.5%, PPV 96%, NPV 8% which was in line with earlier studies which reported WBC sensitivities 67-97.8%, specificities 31.9-90.8%, and PPV 42-91.8%^{14,17-19}.

Also, Narci found cutoff value $10.4 \times 10^3/mm^3$ with 91% sensitivity and 74% specificity⁷.

Dinc found cutoff value $10.6 \times 10^9/\mu L$ with a 73.1% sensitivity and 94% specificity²⁰. CRP is a sensitive acute phase protein that lacks specificity due to increased levels in all acute inflammatory processes, in this study it had significant correlation with acute appendicitis with sensitivity 79% (71%-85%) and specificity 37.5% (10%-74%). Conflict results seen in different studies and our

results differ from those reported by Ulukent et al²¹ who found a sensitivity of 67% and a specificity of 80% and also from Yang et al²² who found sensitivities ranging between 76.5% and 95.6%, specificities ranging between 26.1% and 77.7%, and PPV 95.6²².

Though a meta-analysis examining the accuracy of CRP levels in the diagnosis of acute appendicitis, a wide range of sensitivity (40-99%) and specificity (27-90%) was found in literature²³ which can embrace our results.

In addition, our study reported that the mean CRP level was higher in perforated appendix compared to normal appendix and in some cases it was within normal limits which can be explained by the fact that CRP level starts to increase 12-24 hours after the symptom onset²⁴.

Regarding PDW, our study found no correlation with diagnosis of acute appendicitis, although it was significantly correlated with complicated appendicitis

which was in line with other studies as in a study by Aydogan et al²⁵, in which patients were divided into perforated and non-perforated groups and PDW values were significantly higher in the perforated group. While Bulent et al study showed a diagnostic accuracy of 96% for acute appendicitis²⁶.

The levels of WBC, CRP were all associated significantly with degree of inflammation in appendicitis. A rise in all blood markers was seen in perforated and other complicated appendicitis.

Conclusion: This study showed strong correlation between WBC count and CRP and acute appendicitis with accepted sensitivity but low specificity.

WBC count is most frequently used laboratory test for diagnosis and its value increases with the severity of inflammation and complication particularly in perforated appendicitis. PDW also is helpful in diagnosis of complicated appendix.

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