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Can a Negative C-Reactive Protein Rule out Appendicitis?

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Can a Negative C-Reactive Protein Rule out Appendicitis?

Wadah A Ali ^α, Juanita A Bonila ^σ, Ali A Yammahi ^ρ, Faisal Badri ^ω & Yousif H ElTayeb [¥]

Abstract- Background: Acute appendicitis is one of the commonest causes of acute abdomen. Several studies have looked at the role of C-reactive protein (CRP) and white cell count (WCC) in diagnosing acute appendicitis with varying results but there is a scarcity of such data in the U.A.E. The aim of this study was to determine the sensitivity and specificity of CRP, WCC and neutrophils count in the diagnosis of acute appendicitis.

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Results: Out of 249 patients, 198 (79.5%) were male and 51 (20.5%) were female. The sensitivity and specificity of CRP were 77.31% (CI 71.74%-82.88%) and 51.51% (CI 34.54%-68.48%) respectively. Leukocytosis (WCC $\geq 12 \times 10^9/L$) had a sensitivity of 73.14% (CI 67.26%-79.02%) and a specificity of 51.51% (CI 34.54%-68.48%), whereas a left shift (neutrophils count $\geq 80\%$) showed 66.66% (CI 60.47% - 72.85%) sensitivity and 75.75% (CI 61.23%-90.27%) specificity.

Conclusion: In this study CRP, WCC and neutrophils count showed medium sensitivity and specificity for the histopathological diagnosis of acute appendicitis. This is consistent with other studies and with the wide range of sensitivity and specificity in published literature. Therefore, these tests should always be considered in the light of the clinical context whilst also judiciously utilizing other available resources such as radiological studies.

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1. INTRODUCTION

Acute appendicitis is one of the commonest causes of acute abdomen.^{1, 2} Appendicitis occurs most frequently in the second and third decades of life. The incidence is approximately 233/100,000 population and is highest in the 10 to 19 year-old age group. It is also higher among men (male to female ratio of 1.4:1), who have a lifetime incidence of 8.6 percent compared to 6.7 percent for women.³ Although history and physical examination are of paramount importance in the diagnosis of acute appendicitis many patients do

not have a typical presentation, highlighting the need for laboratory investigations and diagnostic imaging. Delay in diagnosing acute appendicitis is associated with significant morbidity and mortality.

C-reactive protein (CRP) was first discovered in the serum of patients during the acute phase of pneumococcal pneumonia.^{4, 5} it consists of five identical, non-covalently associated subunits, each with a molecular weight of approximately 23 kD, which are arranged symmetrically around a central pore.⁶ CRP and related proteins with this structure are termed pentraxins; others include serum amyloid P and a number of pattern recognition molecules referred to as long pentraxins.⁷ The level of CRP that is truly normal or clinically innocuous is not known. Data from a study conducted by the National Health and Nutrition Evaluation Survey of over 21,000 people revealed that CRP levels vary with age, sex, and race.⁸

Several studies have looked at the role of CRP and white cell count (WCC) in diagnosing acute appendicitis with varying results but there is a scarcity of such data in the U.A.E. In a review of 283 patients, John S et al. concluded that CRP estimation complements clinical diagnosis by a consultant surgeon, and should be included in the diagnostic work-up of acute appendicitis. CRP level estimation yielded a sensitivity of 98% (95% CI 95%-100%) and specificity of 87% (95% CI 73%-94%) and was labeled as an inexpensive test that does not add an undue burden to the cost of management.⁹ Contrastingly, Jangjoo et al found CRP to be neither sensitive nor specific enough to be used as a single test for diagnosing or ruling out acute appendicitis. CRP showed 59% sensitivity (95% CI, 48-69%) and 68% specificity (95% CI, 47-88%).¹⁰

In a meta-analysis of 22 articles and 3436 patients, the sensitivity of CRP ranged from 0.40 to 0.99, and the specificity from 0.27 to 0.90. The cut-off values for a positive test varied from 5 to 25 mg/L. Summary receiver operating characteristic (SROC) curve analysis showed that CRP performed significantly better in acute abdomen populations (11 studies) than in populations already selected for appendectomy (11 studies). The diagnostic accuracy of CRP tended to be a little inferior to that of total leukocyte count (13 studies) CRP was described as a test of medium accuracy in diagnosing acute appendicitis. The distractingly wide range of sensitivity and specificity was attributed to at least in part

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due to variations in cut-off values and to differences in study populations. However, definitive conclusions on the clinical usefulness of the test could not be drawn.¹¹

Another meta-analysis found the sensitivity and specificity of CRP for suspected acute appendicitis to be 57 (39 to 73) and 87 (58 to 97) per cent respectively, compared to 62 (47 to 74) and 75 (55 to 89) per cent for WCC. ROC curve analysis showed that CRP had the highest accuracy (area under ROC curve 0.75, 95 per cent CI 0.71 to 0.78), followed by for WCC (0.72, 0.68 to 0.76) and procalcitonin (0.65, 0.61 to 0.69).¹²

II. MATERIALS AND METHODS

The study was carried out between December 2011 and December 2012. This is a prospectively conducted, retrospectively analyzed study. All adult patients who presented to the emergency department of Rashid Hospital, Dubai with suspected acute appendicitis who subsequently underwent open or laparoscopic appendectomy were the target population. 535 patients underwent appendectomy during the study period (418 laparoscopic and 117 open appendectomies). Immunocompromised patients, pregnant females, patients below 16 and above 60 years of age, those who were managed conservatively and those in which the CRP value was not measured were excluded. Similarly patients in whom the appendix was not removed and presumed normal on gross assessment by the surgeon were excluded from the study. Two hundred and forty nine patients were included in the final analysis.

The patients' preoperative CRP, WCC and neutrophils count values were obtained from the online hospital SAM system (Shared Medical Systems-Albahrain Trading Est Version 2.9.62) and it was compared to the final histopathology. A CRP value of 10mg/dL or more was considered positive and similarly a cut off of $12 \times 10^9/L$ was set for the white cell count. A left shift was considered present when the neutrophils count was above 80 percent. The histopathology result was categorized into either positive or negative for acute appendicitis. A third category was added where the appendix was negative on histopathological examination but there was an alternative surgical diagnosis intra operatively. This data was recorded in a special questionnaire.

The statistical analysis was performed on all collected data using SPSS programme to calculate the sensitivity and specificity of elevated C-reactive protein, white cell count and neutrophils count.

III. RESULTS

535 patients underwent appendectomy during the study period (418 laparoscopic and 117 open appendectomies) (Figure 1). Immunocompromised patients, pregnant females, patients below 16 and

above 60 years of age, those who were managed conservatively and those in which the CRP value was not measured were excluded. Similarly patients in whom the appendix was not removed and presumed normal on gross assessment by the surgeon were excluded from the study. Two hundred and forty nine patients were included in the final analysis (198 male and 51 females) (Figure 2). The mean age was 30.06 years. The overall rate of non therapeutic (negative) appendectomies was 13.25% (Figure 3). The sensitivity and specificity of CRP were 77.31% (CI 71.74%-82.88%) and 51.51% (CI 34.54%-68.48%) respectively. Leukocytosis ($WCC \geq 12 \times 10^9/L$) had a sensitivity of 73.14% (CI 67.26%-79.02%) and a specificity of 51.51% (CI 34.54%-68.48%). A left shift (neutrophils count $\geq 80\%$) showed 66.66% (CI 60.47% - 72.85%) sensitivity and 75.75% (CI 61.23%-90.27%) specificity (Figure 4). The positive predictive value for CRP was 91.25% while the negative predictive value was 25.75%. The positive and negative predictive values for WCC were 90.80% and 22.66% respectively. The positive predictive value for neutrophils left shift was 94.73% and the negative predictive value was 25.77%. When male patients were considered separately, the sensitivity and specificity for CRP were 76.96% (CI 70.77%-83.15%) and 55% (CI 32.27%-76.73%) respectively compared to 78.94% (CI 75.97%-91.91%) and 46.15 (CI 19.07%-73.23%) in females (Figure 5).

The positive and negative likelihood ratios for CRP were 1.59 and 0.44 respectively compared to 1.50 and 0.52 for WCC and 2.74 and 0.44 for neutrophils count.

IV. DISCUSSION

Appendectomy is one the most commonly performed abdominal operations. Delay in the diagnosis of acute appendicitis is associated with significant morbidity and mortality. The negative appendectomy rate in published literature remains 15-30% despite of the range of available laboratory and imaging tests. Several studies have looked at the sensitivity and specificity of CRP and WCC in the diagnosis of acute appendicitis with somewhat conflicting results. In one meta analysis the sensitivity of CRP ranged from 0.40 to 0.99, and the specificity from 0.27 to 0.90¹¹. This wide range was attributed in part to the different cut off values used in the measurement of CRP and the different study populations. In this study CRP, WCC and neutrophils count showed medium sensitivity and specificity for the histopathological diagnosis of acute appendicitis. This is consistent with other published studies^{11,12} and with the wide range of sensitivity and specificity in published literature.⁹⁻¹² At 77.31%, CRP showed a slightly superior sensitivity when compared to WCC (73.14%) and neutrophils count (66.66%) while neutrophils count was the most specific of the three tests (75.75%). The positive likelihood ratio of CRP was 1.59, that is to say a

person with acute appendicitis is about 1.5 times more likely to have a positive test than a person who does not have the condition. It is worthwhile to mention that in four cases where both the CRP and WCC were positive and the histopathology was negative for appendicitis, there was an alternative intra operative diagnosis (perforated duodenal ulcer, ischemic bowel, carcinoid tumour of the appendix and a ruptured ovarian cyst) which required surgical intervention. Therefore, these tests should always be considered in the light of the clinical context whilst also judiciously utilizing other available resources such as radiological studies. Asfar S

et al concluded that a normal pre-operative CRP measurement in patients presenting with suspected acute appendicitis is mostly associated with a normal appendix and that deferring surgery in these patients would probably reduce the rate of unnecessary appendectomies¹³; the authors of this study disagree with this conclusion. Our findings suggest that a negative CRP and an absence of leukocytosis do not completely exclude a diagnosis of acute appendicitis, this is to be kept in mind when evaluating patients presenting with acute abdomen.

Figures

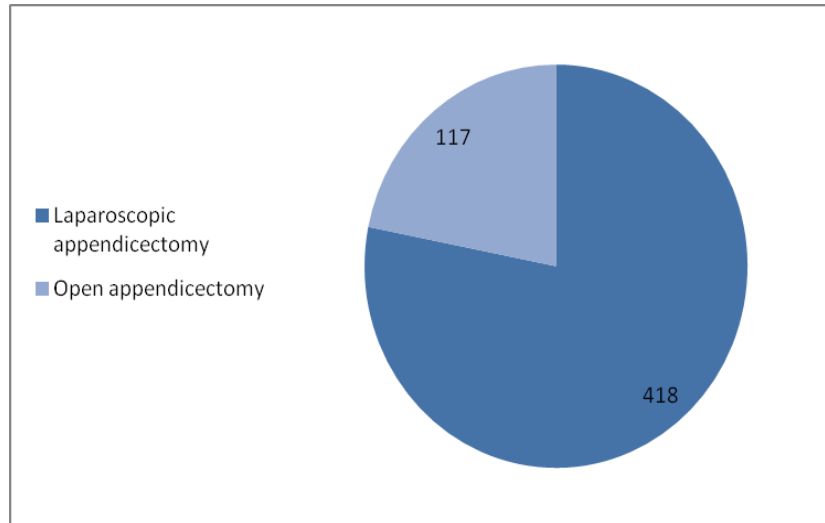


Figure 1 : Total appendectomies: 535

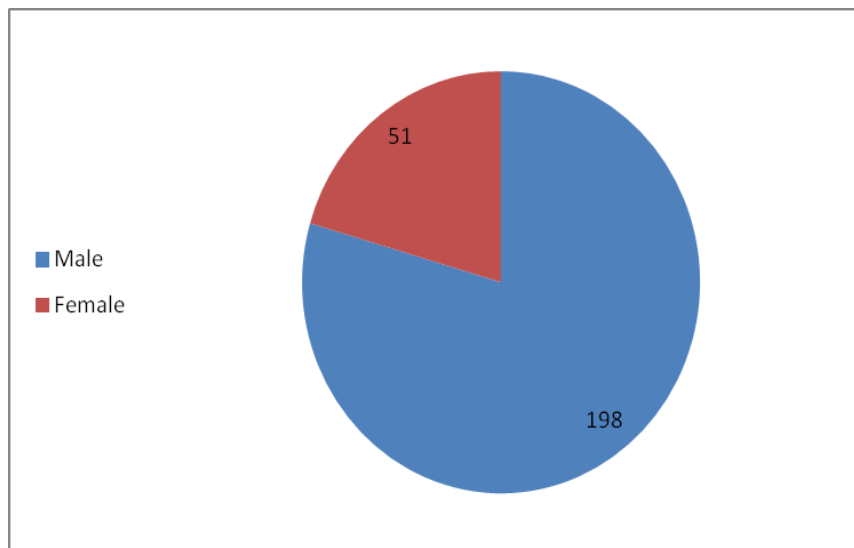


Figure 2 : Gender distribution

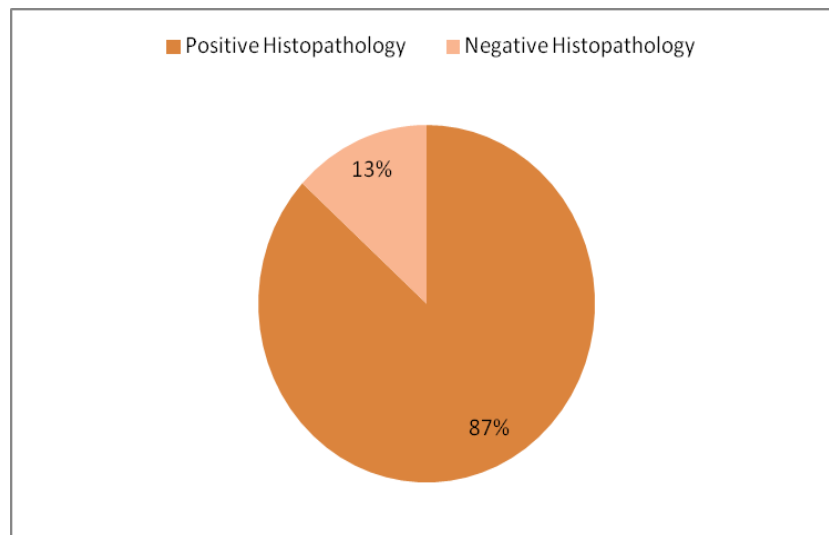


Figure 3 : Negative appendicectomy rate

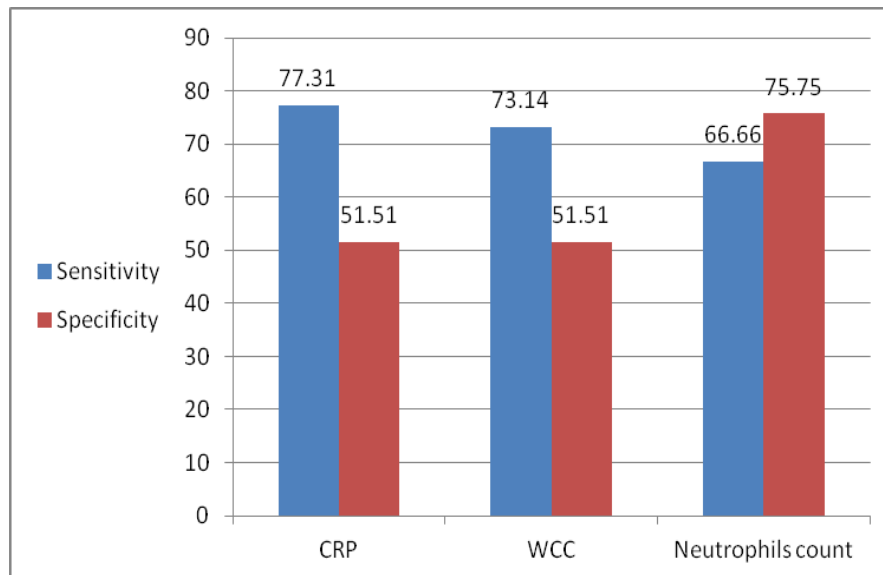


Figure 4 : Sensitivity and Specificity

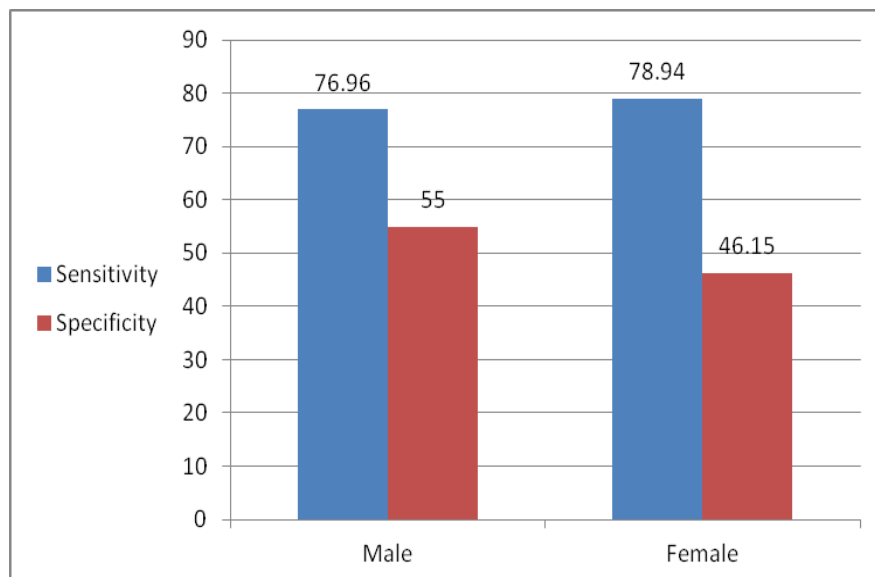


Figure 5 : CRP Sensitivity and Specificity Males /Females

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