

# C-reactive protein as a predictor of severity of appendicitis

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**Background:** Complex (perforated or gangrenous) appendicitis has a high rate of morbidity in South Africa.

**Objectives:** To determine if CRP is superior to WCC in diagnosing complex appendicitis. Determining an optimal cut-off value for CRP in detecting complex appendicitis.

**Methods:** The study retrospectively reviewed results from January 2013 to December 2015 at Paarl Hospital in the Western Cape province. All patients who had their appendices surgically removed due to suspected appendicitis and who had preoperative results for CRP and WCC were included. Using the area under the Receiver Operated Characteristics curve we compared the inflammatory markers of 2 groups with histologically proven appendicitis: those with complex (perforated or gangrenous appendix) and those with uncomplicated appendicitis (inflamed appendix). Youden's J statistic was used to determine the optimal cut-off value above which complex appendicitis would be the most likely diagnosis.

**Results:** A total of 591 patients were identified, 385 had results for both WCC and CRP. CRP (AUC 72%) proved to be a fair and WCC (AUC 58%) a poor predictor of complex appendicitis. Cut-off values for CRP and WCC were found to be 215 mg/l and  $16.80 \times 10^9$  cells/l respectively. At these threshold values CRP (sensitivity 51.4%, specificity 85.7%, p-value < 0.001, positive predictive value 80.2%, negative predictive value 61%, positive likelihood ratio 3.6 and diagnostic odds ratio 6.35) proved to be much better than WCC (sensitivity 43%, specificity 73.8%, p-value = 0.022, positive predictive value 64.9%, negative predictive value 53.4%, positive likelihood ratio 1.64 and diagnostic odds ratio 2.11) in predicting complex appendicitis.

**Conclusion:** CRP is superior to WCC in the differentiation between uncomplicated and complex appendicitis. Using a cut-off value of CRP 215 mg/l is statistically significant in diagnosing complex appendicitis. This value should be used cautiously as many more studies are needed to confirm these findings.

S Afr J Surg 2017;55(2)

## Introduction

Appendicitis is the most common intra-abdominal emergency worldwide.<sup>1</sup> In South Africa appendicitis is associated with higher morbidity than in the developed world.<sup>2</sup> A recent systematic review looked at a number of studies done on appendicitis in South Africa. This study found that a high perforation rate (36%) attributes to the burden of disease.<sup>3</sup> Another South African study published in 2015 reviewed a total of 1004 patients with appendicitis and found that 60% had perforated appendices.<sup>4</sup> These figures are generally attributed to difficulty in accessing healthcare and delay in presentation.<sup>2</sup> Promptly and accurately diagnosing and treating appendicitis has its complexities. Many differentials need to be excluded and patients need to be prioritized for surgical intervention based on severity of disease. The prompt and accurate management of patients with appendicitis remains a priority in decreasing the morbidity rate.

The diagnosis of appendicitis is mainly clinical although inflammatory markers, ultrasound (US) and computerized tomography (CT) may aid in the diagnosis. In our setting C-reactive protein (CRP) and white cell count (WCC) are commonly used as the inflammatory markers to aid in the diagnosis and to determine the severity of disease. CT and US are utilized but are less readily available after hours and operator dependent.

In a South African setting with a high perforation rate, we investigate CRP as a quantitative measure of severity of appendicitis. A raised CRP in appendicitis has not only been shown to be a good predictor of appendicitis but is also directly related to the severity of the inflammation.<sup>5</sup>

## Objectives

The main aim of this study is to determine if CRP can be used to differentiate between complex (gangrenous or perforated)

and non-complicated appendicitis. The secondary objective is to determine a threshold value of CRP above which the appendicitis may be regarded as complex.

## Methods

Paarl Hospital caters to the general hospital and emergency care needs of a population of over 600 000 in a vast geographical area of approximately 22 500 square kilometers encompassing a predominantly semi-rural region 60 km away from Cape Town.<sup>6</sup> It forms part of the public healthcare system and functions as a secondary level care facility. Primary level care facilities in the described area will refer patients with suspected appendicitis to Paarl Hospital. Patients can also present themselves to the 24-hour emergency unit at Paarl Hospital. The scope of emergency surgery includes penetrating or blunt chest and abdominal trauma, abdominal emergencies (such as bowel perforations and obstruction), hernias, upper and lower gastrointestinal bleeding, pancreatitis, appendicitis, burns wounds and basic chronic vascular pathology. Patients requiring care outside of the scope provided by Paarl Hospital will be fast-tracked to the tertiary level care facility. One operating theatre is dedicated to providing emergency surgery 24 hours daily. This operating theatre is shared by all surgical departments in the hospital (Obstetrics, Orthopaedics and General Surgery).

Retrospectively we identified all patients who underwent surgery for clinically diagnosed acute appendicitis at Paarl Hospital. Patients eligible for inclusion were admitted with a clinical suspicion of appendicitis and received an appendectomy between January 2013 and November 2015. The diagnosis and management plan was determined by the attending surgeon. We excluded patients treated nonoperatively and those who underwent routine appendectomy. Furthermore, patients with a histologically proven noninflamed appendix, malignancy of the appendix or parasitic infection were excluded. This way we obtained a group with retrospective histologically proven appendicitis. This group was further subdivided into 2 groups:

- Uncomplicated appendicitis:  
Histologically proven inflammation of the appendix without signs of necrosis and perforation.
- Complex appendicitis:  
Histologically proven necrosis or perforation of the appendix.

For the purpose of this study we compared the peripheral venous blood (WCC and CRP drawn on the first presentation to our health facility) to the outcome of the 2 groups (with their respective histopathology). Thus patients with missing data (CRP, WCC or histopathology) were excluded from the study. Approval to perform the study was obtained from the Western Cape Department of Health Research and ethical approval obtained from the Health Research Ethics Committee of Stellenbosch University.

## Statistical analysis and model

Statistical analysis was used to compare the predictive capabilities of CRP and WCC in differentiating between complex and non-complicated appendicitis. The Mann-Whitney U-test was performed to identify any significant differences between complicated and non-complicated appendicitis. An optimal cut-off value for the severity of appendicitis was calculated using the Receiver-operating characteristics (ROC) analysis. Table 2 shows the accuracy measurements of CRP and WCC in diagnosing complicated appendicitis. An optimal cut-off point was detected using Youden's J statistic. The statistical software R was used for the statistical analysis of the data. The values of the laboratory parameters were expressed as mean +/- standard deviation (SD). With a p-value < 0.0001 all results were considered to be very significant.

## Results

A total of 591 patients underwent a surgical procedure for the clinical diagnosis of acute appendicitis at Paarl Provincial Hospital. After excluding the patients with missing blood results or histopathology results, the sample size was reduced to 385 patients. Of these patients 210 were male and 175 female with age ranging from 2 – 75 years (mean age of 26.74 years). Uncomplicated appendicitis occurred in 126 cases, 142 had complex appendicitis and 117 did not have appendicitis.

There was a large deviation in the laboratory marker values. We obtained CRP measurements of 115 +/- 106 mg/l and 210 +/- 130 mg/l for uncomplicated and complex appendicitis respectively. Similar deviations were found for WCC, with measurements of 14.96 +/- 5.71 10<sup>9</sup> cells/l and 16.90 +/- 7.22 10<sup>9</sup> cells/l for uncomplicated and complex appendicitis respectively (Table 1).

Using ROC analysis, CRP proved to have a much greater

**Table 1: CRP and WCC results for the two groups**

	Uncomplicated appendicitis (value +/- SD)	Complex Appendicitis (value +/- SD)
CRP (mg/l)	115 +/- 106	210 +/- 130
WCC ( 10 <sup>9</sup> cells/l)	14.96 +/- 5.71	16.90 +/- 7.22

SD = Standard Deviation

ROC curves for CRP and WCC

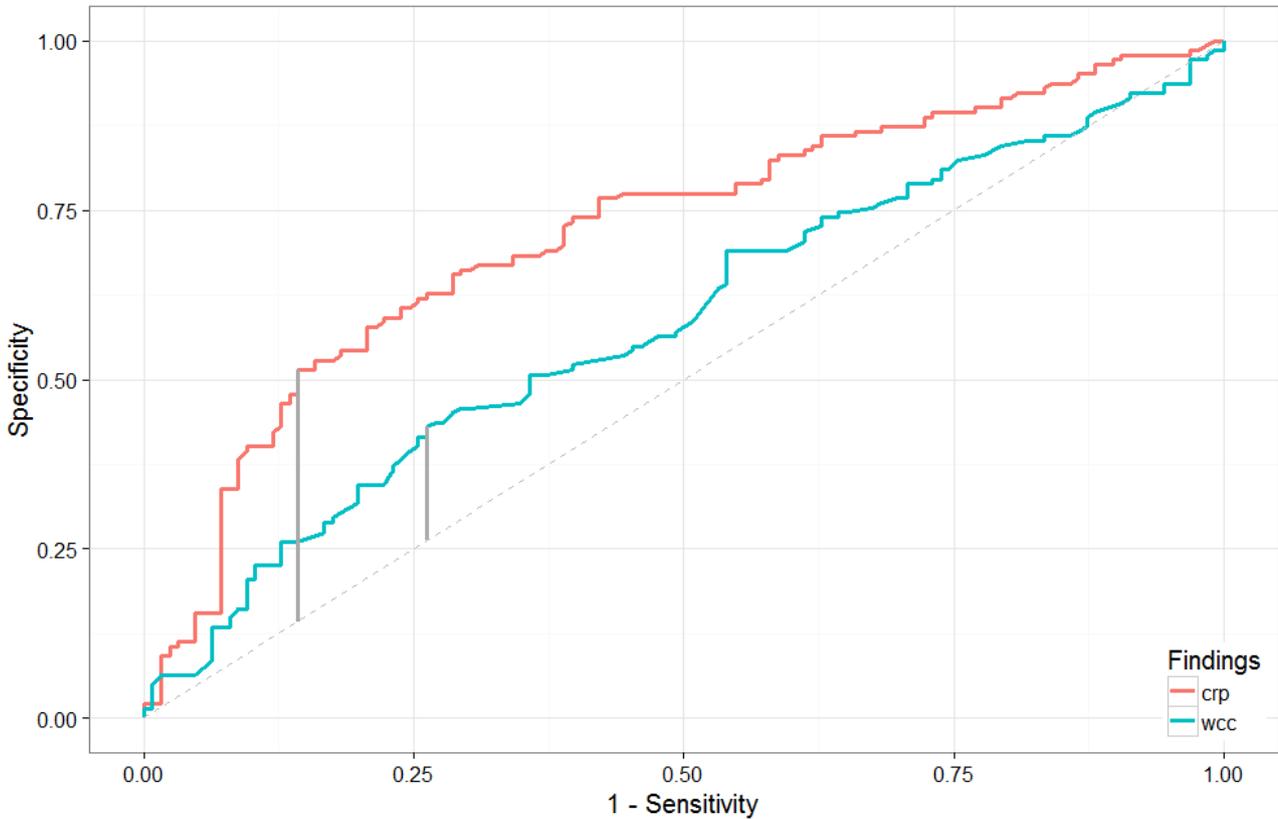


Figure 1. ROC curve for CRP and WCC. (ROC = receiver operating characteristic curve, CRP = C-reactive protein, WCC = white cell count).

diagnostic accuracy compared to WCC. Where CRP was a fair indicator distinguishing between uncomplicated and complex appendicitis (area under curve 0.72), WCC failed at distinguishing between these 2 groups (area under curve for WCC 0.58).

The maximal value of the Youden’s J statistic was 0.37 for CRP and 0.17 for WCC respectively. These values coincide with cut-off values of CRP 215 mg/l and WCC 16.80 10<sup>9</sup> cells/l (Figure 1).

Using these cut-off values, we calculated the diagnostic accuracy for each value. WCC of 16.80 10<sup>9</sup> cells/l had a sensitivity 42.96%, specificity 73.81%, p-value = 0.022, positive predictive value 64.89%, negative predictive value 53.45%, positive likelihood ratio 1.64 and a diagnostic odds ratio 2.11. CRP of 215 mg/l showed a sensitivity 51.41%, specificity 85.71%, p-value < 0,001, positive predictive value 80.22%, negative predictive value 61.02%, positive likelihood ratio 3.60 and diagnostic odds ratio 6.35 (Table 2). These results show that if the value of CRP was above 215mg/l it was very likely to be complex and not uncomplicated appendicitis. Even though the cut-off value for WCC is statistically significant the p-value of CRP is 2 orders of magnitude smaller and serves as a better marker in distinguishing complex and uncomplicated appendicitis.

Table 2: Accuracy measures associated with cut off values

	WCC (16.80 10 <sup>9</sup> cells/l)	CRP (215 mg/l)
sensitivity	42.96%	51.41%
specificity	73.81%	85.71%
P-value	0.022	< 0.001
Positive predictive value	64.89%	80.22%
Negative predictive value	53.45%	61.02%
Positive likelihood ratio	1.64	3.60
Diagnostic odds ratio	2.11	6.35

## Discussion

In our setting where CT and US are not always readily available, we rely on inflammatory markers to aid in the decision of management after a clinical diagnosis of acute appendicitis is made. We manage both uncomplicated and

complex appendicitis operatively. The question of whether the inflammatory markers can differentiate between these two groups adds value to the surgeon's expectations of the surgery and timing of the surgery. CRP was a fair predictor to differentiate between uncomplicated and complex appendicitis. WCC failed to differentiate between these 2 groups.

We also suggest a cut-off value for CRP and WCC to predict the likelihood of complex appendicitis. Yokoyama et al. suggest a significance level cut-off value for CRP (50 mg/l) that predicts the likelihood of complex appendicitis.<sup>7</sup> This can be used to aim the management of a patient. Appendectomy remains the gold standard for managing appendicitis although antibiotic therapy has been suggested for the treatment of acute uncomplicated appendicitis of low risk patients, however recurrence remains a risk.<sup>8,9</sup> This study found a larger cut-off value, CRP 215 mg/l. Above this threshold the likelihood of complex appendicitis increases. These results should be taken into account in prioritizing the urgency of surgical management.

Comparing the development of clinical scores used to diagnose acute appendicitis, one can see superior diagnostic abilities when obtaining a CRP level.<sup>10</sup> Additionally, it is also important to consider the timing of CRP value compared to the duration of symptoms.<sup>11</sup> Data in this study lacked the duration of symptoms before the peripheral venous blood was drawn. This influences the laboratory value of the inflammatory markers and is an area of improvement in future studies.

## Conclusion

In this study CRP is found to be superior to WCC in the differentiation between uncomplicated and complex appendicitis. Using a cut-off value of CRP 215 mg/l was statistically significant in diagnosing complex appendicitis but should be used carefully as many more studies are needed to determine an optimal cut-off value.

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