



# Computed tomography in adults with atypical clinical presentation of acute appendicitis: comparison of findings with inflammatory serum markers

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## Abstract

**Purpose:** To evaluate both the potential usefulness of multidetector computed tomography (MDCT) in diagnosis of acute appendicitis (AA) in patients with atypical clinical presentation and to compare findings with C-reactive protein (CRP) and white cell count (WCC).

**Materials and methods:** MDCT images in 69 patients with atypical presentation of AA were retrospectively reviewed by two readers in consensus. Diagnostic accuracy, sensitivity, specificity, positive and negative predictive values (PPV/NPV) were assessed considering histopathological evaluation as reference. Patients with AA were grouped in nonperforated vs perforated and CRP/WCC were correlated using both Chi-square-test ( $\chi^2$ ) and receiver operating characteristic (ROC) curve analysis.

**Results:** 39 patients underwent surgery and AA was confirmed histopathologically in 29/39 cases (74.4%), showing nonperforated AA (n=23, 79.3%) and perforated AA (n=6, 20.7%). In the remaining 10/39 patients (25.6%) diverticulitis of sigmoid colon was diagnosed (n=3); colitis (n=4); cholecystitis (n=3). Among the other 30/69 patients MDCT was either unremarkable (n=18) or differentials were detected (n=12). Diagnostic accuracy in patients with histopathologically confirmed AA was 95.7%, sensitivity was 90.6%, specificity was 93.6%, PPV was 83.0%, and NPV was 89.8%. All MDCT findings but calcified appendicoliths and CRP/WCC correlated statistical significant when AA was confirmed histopathologically ( $\chi^2=26.2$ ;  $p<0.001$ ). In contrary to WCC ( $p=0.11$ ), CRP was significantly higher in patients with perforated AA than nonperforated AA ( $p<0.01$ ), demonstrating an optimal cut-off value  $>121.5$  mg/L.

**Conclusion:** MDCT is required immediately to rule out perforation in patients with suspected AA despite atypical clinical presentation and a CRP level  $>121.5$  mg/L.

**Keywords:** Appendicitis, multidetector computed tomography, c-reactive protein, white cell count

## Introduction

Acute appendicitis (AA) is the most common cause of acute abdominal pain in adults [1,2]. 70% of patients have classical clinical features such as pain near the umbilicus that grows more intense over time and shifts to the right lower quadrant (RLQ), fever, and guarding at McBurney's point [3]. Those classical cases allow making a quick and safe diagnosis by patient's history, physical examination and elevated C-reactive protein (CRP) and white cell count (WCC) in serum analysis. In the remaining 30% of the cases at least one of these classical findings is absent (the so-called atypical presentation of AA) [4]. These patients usually present with moderate abdominal pain that does not worsen or shift. Atypical clinical presentation of appendicitis is more frequent in certain patient groups (elderly, pregnant women, and particularly in patients with anatomical variations of the vermiform appendix relative to the cecum) and may result in diagnostic confusion, and risk of complication such as appendiceal perforation with abscess formation, peritonitis,

and bowel obstruction [4-6]. A prompt diagnosis is rewarded by marked decrease in morbidity and mortality [7].

Multidetector computed tomography (MDCT) is well established for the diagnosis of AA in adults in several countries, e.g., the United States [8], showing a sensitivity of 90-100%, a specificity of 90-99.1%, a positive predictive value (PPV) of 90-95.7%, and a negative predictive value (NPV) of 90-100%, respectively [1,9,10]. MDCT is superior to transabdominal ultrasound in the diagnosis of appendicitis [11]. Signs of AA on MDCT are a thickened appendiceal wall above 2 mm with ring-like contrast enhancement, a cross-sectional diameter above 6 mm, periappendiceal fat attenuation, a calcified appendicolith, and abscess formation in the RLQ [12-16].

In case of suspected AA taking of a blood sample is an important part of the clinical evaluation. But the diagnostic value of CRP and WCC remains a controversial issue as recent studies showed low diagnostic accuracy in AA for these inflammatory serum markers [17,18]. However, CRP and WCC cannot be relied



**Figure 1.** Axial MDCT image in a 75-year-old woman with perforated acute appendicitis demonstrates a calcified appendicolith (arrow) and a well-defined periappendiceal abscess (asterisk). Serum C-reactive protein level was 250 mg/L and white cell count was  $15.5 \times 10^9/L$ .

upon to make a specific diagnosis, but the inflammatory markers may be helpful in clinical decision making in those patients. None the less, a considerable amount of investigators constrain their diagnostic decisions based on whether the inflammatory serum markers are either elevated or not [19,20].

A recent retrospective study evaluated the relationships between the severity of AA in patients with typical presentation as detected on MDCT and CRP/WCC [21]. CRP was found to correlate with MDCT determined stage of appendiceal inflammation and could be a predictor for perforation, where as WCC might be useful to detect early AA [21].

As far as we know, there have been no reports about the diagnostic accuracy of MDCT in the detection of AA in patients with atypical clinical presentation only, having regard to the comparison between MDCT findings and the inflammatory serum markers. Therefore, the aim of our study was both to assess the value of MDCT in the diagnosis of AA in patients with atypical clinical presentation and to determine the optimal cut-off value of CRP/WCC for histopathologically proven perforation.

## Materials and methods

### Patient population

487 patients with typical clinical features of AA underwent emergency appendectomy without a preoperative MDCT scan in our university medical center between January 2009 and January 2012. The study group consisted of 69 consecutive patients (33 males; 36 females; age  $54 \pm 17.4$  years; range 18-90 years) with atypical clinical features of AA who had been referred for a MDCT scan during the same period of time. Subjects were selected according to the following inclusion and exclusion criteria:

### Inclusion criteria

1. Criteria for atypical presentation of AA were:
  - mild to moderate abdominal pain that did not grow in intensity.
  - absence of at least one of the classic findings of AA: pain near the navel that shifts in the RLQ ( $n=45$ ), fever ( $n=5$ ), and local tenderness and guarding at McBurney's point ( $n=28$ ).
  - diffuse mild touch-sensitivity of the abdomen on the physical examination.
2. All women had normal findings in the gynecologic examination.
3. Histopathology results were available in patients who under went surgery immediately after the MDCT scan.
4. Image data was digitally available for retrospective analysis in our radiological information system (RIS).

### Exclusion criteria

1. Pregnant women and children
  - The study protocol has been approved by the local Clinical Institutional Review Board and complied with the Declaration of Helsinki. All subjects had given written informed consent for the retrospective evaluation of their data.

### MDCT acquisition and image reconstruction

MDCT images were obtained using a 256-detector row CT scanner (Brilliance iCT; Philips Medical Systems, Best, the Netherlands). Patients were given 120 mL iomeprol (Imeron 300; Bracco, Konstanz, Germany) intravenously at a rate of 3 mL/sec via the antecubital vein. All MDCT examinations were performed without enteric (oral or rectal) contrast agents. Imaging in inspiration started after 110 seconds from the diaphragm to the pubic symphysis (120 kV, 80 mA, transaxial field of view 350 mm, no gap, collimation 2 mm x 128 mm x 0.625 mm, pitch 0.985, gantry rotation time 0.33 s). The radiation dose was adjusted according to the patients' body size and body shape by automatic current selection (ACR; Dose-Right©; Philips Healthcare, Best, the Netherlands). Transaxial, sagittal, and coronal images were reconstructed from isotropic voxels with a slice thickness of 3 mm [22].

### Image analysis

The transaxial and coronal MDCT images were evaluated independently by two readers (4 and 5 years of experience in abdominal imaging, respectively) blinded to all subjects' clinical information at a window range of 60-340 Hounsfield units (HU) on state-of-the-art GE Centricity RIS/PACS workstations. In case of disagreement between the two readers, who were aware that this was a study to diagnose AA, consensus was reached on a final reading for the statistical analyses [23].

MDCT images were visually evaluated for the presence of various appendicitis signs [12-16]:



**Figure 2.** Axial (a) and coronal (b) MDCT images in a 45-year-old man show an appendiceal wall thickening (>2 mm) with a cross-sectional diameter of 12 mm (arrows), and periappendiceal inflammatory changes. Serum C-reactive protein level was 140 mg/L and white cell count was  $14.5 \times 10^9/L$ .

1. Periappendiceal abscess formation (Figure 1).
2. Wall thickness above 2 mm with ring-like contrast enhancement (Figure 2a).
3. Increased cross-sectional diameter above 6 mm (Figure 2b).
4. Periappendiceal fat attenuation (Figures 2a and 2b).
5. Calcified appendicolith (Figure 1).

The first sign was used to detect appendiceal perforation. The combination of second, third, and fourth sign was used to diagnose nonperforated AA. The latter sign was considered as a secondary finding, and was not pathognomonic for the diagnosis of AA [24], especially when it was seen on MDCT images without appendiceal wall or adjacent fat abnormalities.

### Histopathological evaluation

All surgical specimens were analyzed by pathologists with more than 5 years of experience. The histopathological diagnosis was based on changes and density of neutrophil, lymphocyte and eosinophil infiltration in the appendiceal wall. The severity of appendiceal inflammation was grouped in 4 histopathological conditions: phlegmonous, ulcero-phlegmonous, gangrenous, and perforation with abscess formation.

### Laboratory findings

Blood samples were taken from the antecubital vein from all patients. Markers of inflammatory conditions were elevated WCC (normal range:  $4.5-10 \times 10^9/L$ ) and elevated CRP (normal range: <5 mg/L). Blood values were illustrated using box plot graphs.

### Statistical analysis

The diagnostic accuracy, sensitivity, specificity, and positive and negative predictive value (PPV/NPV) of the MDCT findings were

analysed using a contingency table. The Chi-square test ( $\chi^2$ ) was used to compare MDCT findings with mean inflammatory serum markers. Continuous variables were expressed as mean  $\pm$  SD. For between-group comparisons of continuous data, p-values were calculated from Mann-Whitney's U test for unpaired samples. Receiver operating characteristic (ROC) analysis was performed to define the optimal cut-off value for CRP. Statistical significance was established for 2-tailed p-values of less than 0.05. Data collection and statistical calculations were performed using SPSS Statistics 21 (IBM Inc. SPSS Statistics) software.

### Results

#### MDCT findings and histopathological analysis in the study group

Evaluation of MDCT scans was feasible in all 69 patients. AA was diagnosed in 32 patients (46.4%) on MDCT using the defined signs of appendicitis. 39/69 patients (56.5%) underwent emergency surgery (including all MDCT-positive patients) immediately after the diagnosis was made by MDCT examination. In these cases, histopathology confirmed the diagnosis of AA in 29/39 patients (74.4%). The three remaining MDCT-positive patients (4.3%) were false-positive with a final diagnosis of perforated diverticulitis of the sigmoid colon. In those patients the appendix could not be identified retrospectively, because of abscess formation in the RLQ.

In the remaining 7/39 patients (17.9%) who underwent surgery, ischemic colitis was diagnosed on MDCT in 4 patients (10.2%); and acute cholecystitis in 3 patients (7.7%) with histopathologically confirmation, respectively. Among the remaining patients, who did not undergo surgery (30/69), colitis was diagnosed on MDCT (n=5); urolithiasis (n=3); pyelonephritis (n=2), pancreatitis (n=2), and MDCT was unremarkable (n=18). None of these patients presented later with AA in our hospital.

#### MDCT findings in patients with histopathologically confirmed AA

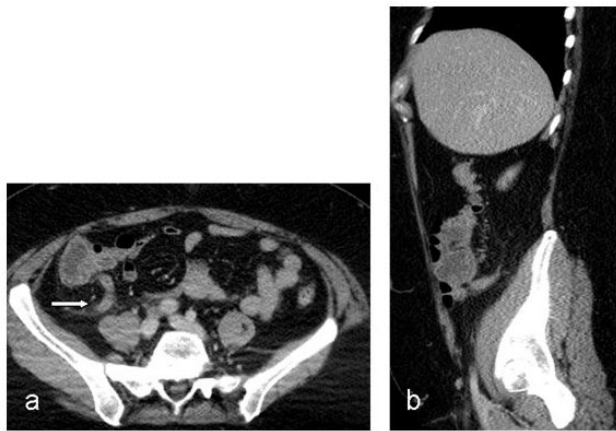
In the 29 patients with histopathologically proven AA MDCT revealed nonperforated AA in 23 cases (79.3%). All of them showed a thickened appendiceal wall above 2 mm with ring-like contrast material enhancement, a cross-sectional appendiceal diameter above 6 mm, and periappendiceal fat attenuation. In the remaining 6 cases (20.7%) appendiceal perforation with abscess formation in the RLQ was correctly identified with MDCT. A calcified appendicolith (n=5) was found in patients with nonperforated AA as well as perforated AA.

Furthermore, the position of the inflamed appendix corresponded to the McBurney's point (n=13), retrocecal (n=9) (Figures 3a and 3b), periumbilical (n=3) (Figures 4a and 4b), retroileal (n=2), pelvic (n=1), and subcostal (n=1).

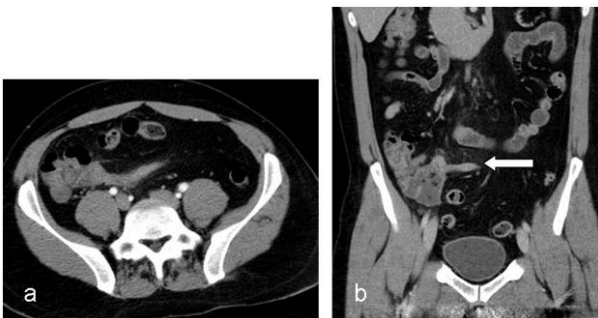
#### Laboratory findings

In 23/29 patients (79.3%) with nonperforated AA inflammatory





**Figure 3.** Retrocecal location of the inflamed appendix (arrow) in a 76-year-old man. Axial (a) and sagittal (b) MDCT images show a periappendiceal edema. Serum C-reactive protein level was 88 mg/L and white cell count was  $11.5 \times 10^9/L$ .

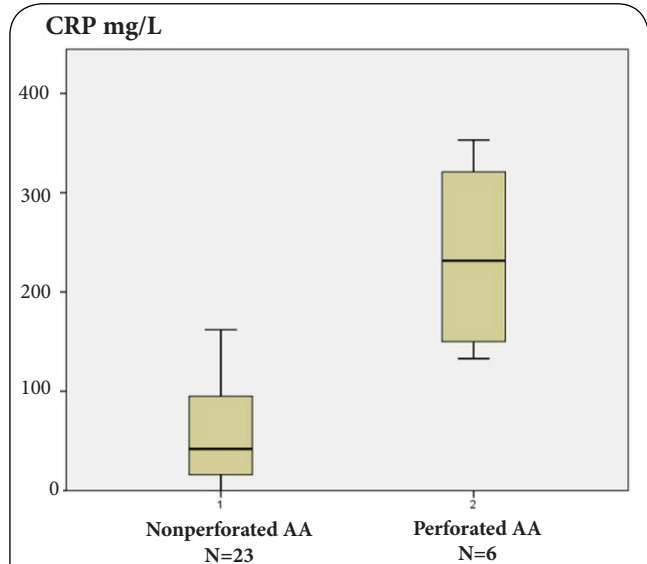


**Figure 4.** 29-year-old man with pain around the umbilicus that does not worsen or shift. Axial (a) and coronal (b) MDCT images demonstrate a long inflamed appendix with the tip located periumbilical (arrow). Serum C-reactive protein level was 85 mg/L and white cell count was  $13.9 \times 10^9/L$ .

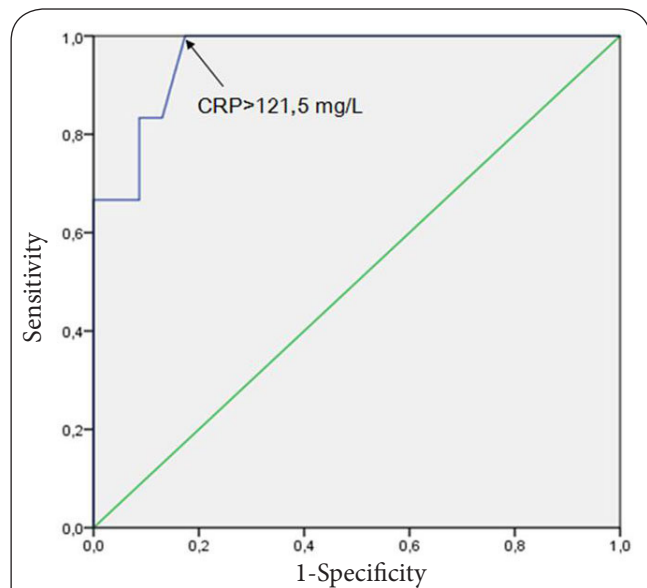
serum markers were slightly increased (mean CRP  $58.7 \text{ mg/L} \pm 53.3$ ; range 0–162/mean WCC  $11.7 \times 10^9/L \pm 2.1$ ; range 7.2–16.6). Of them, 1 patient only had an elevated level of CRP, and 1 only leukocytosis. In all 6/29 patients (20.7%) with perforated AA CRP was highly elevated (mean CRP  $237 \text{ mg/L} \pm 92.3$ ; range 133–353), and mean WCC was moderately elevated (WCC  $13.2 \times 10^9/L \pm 1.4$ ; range 11.5–14.7). In 3/32 MDCT-positive patients with a final diagnosis of perforated diverticulitis of the sigmoid colon CRP levels were highly elevated (mean CRP  $177.3 \text{ mg/L} \pm 24.0$ ; range 143–212).

**Statistical analysis with histopathological correlation**

Statistical analysis revealed diagnostic accuracy of 95.7%, sensitivity of 100%, specificity of 93.6%, PPV of 83.0%, and NPV of 89.8% in the diagnosis of AA using MDCT. Inflammatory serum

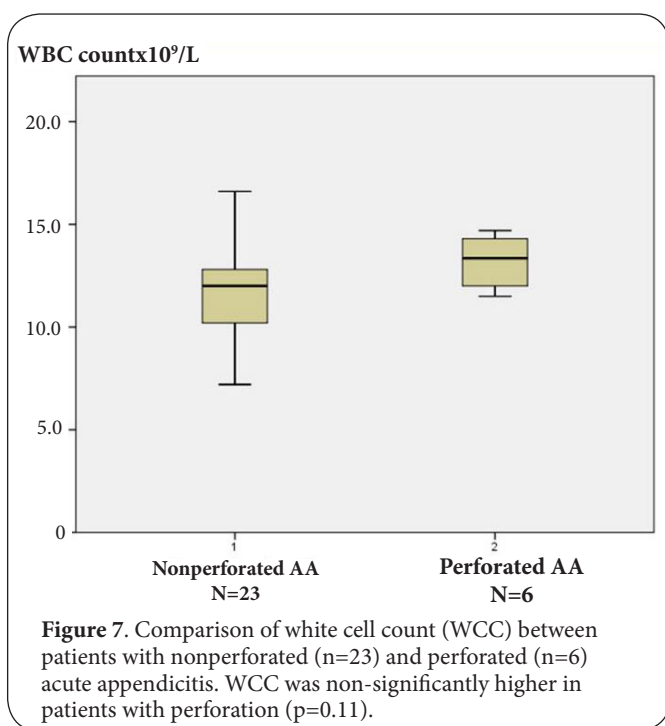


**Figure 5.** Comparison of C-reactive protein (CRP) between patients with nonperforated (n=23) and perforated (n=6) acute appendicitis. CRP was significantly higher in patients with perforation ( $p < 0.01$ ).



**Figure 6.** Receiver-operating characteristic curve for assessment of abscess due to appendiceal perforation as determined by serum C-reactive protein levels (AUC 0.96).

markers and all MDCT findings but calcified appendicoliths correlated statistical significant when AA was confirmed histopathologically ( $\chi^2=26.2$ ;  $p < 0.001$ ). CRP levels (Figure 5) were significantly higher for perforated AA than for non-perforated AA ( $231.5 \pm 92.3$  vs  $42 \pm 53.3$ ,  $p < 0.01$ ). ROC analysis showed that the optimal threshold for differentiation of nonperforated and perforated AA was a CRP level  $> 121.5 \text{ mg/L}$



(AUC 0.96) (Figure 6), resulting in a sensitivity of 100% and a specificity of 82.6% for a 95% confidence interval: 0.892 to 1.000 with a standard error of 0.35. WCC (Figure 7) was non-significantly higher for perforated AA than for nonperforated AA (13.4±1.4 vs 12±2.1, p=0.11).

## Discussion

Our results demonstrate high diagnostic accuracy of MDCT in the diagnosis of AA in patients with atypical clinical presentation, particularly in the detection of abscess formation in the RLQ. In patients with nonperforated AA (n=23) CRP and WCC were slightly elevated (except of 2 cases with normal levels of CRP or WCC, respectively). When appendiceal perforation was histopathologically confirmed (n=6), CRP was highly elevated showing an optimal cut-off point more than 121.5 mg/L (p<0.01). In contrast, WCC was moderately raised and the cut-off point was non-significantly (p=0.11).

These findings suggest that further diagnostic workup is immediately required in those patients to reduce both complication and negative appendectomy rate. But not all patients should undergo MDCT regarding the radiation dose and the costs. We recommend the following diagnostic algorithm to confirm or r/o AA: When AA is diagnosed on transabdominal ultrasound and moreover, CRP levels are higher than 121.5 mg/L patients should undergo urgent appendectomy. When transabdominal ultrasound was not groundbreaking, gynecologic examination should be performed principally in women to exclude differential diagnosis such as adnexitis or tubo-ovarian abscess.

Furthermore, abdominal magnetic resonance imaging (MRI) without contrast administration is the method of first choice in women in childbearing age and pregnant women (hence, we excluded pregnant women from our study) with persistent suspicion of AA [25]. Additionally, MRI should be performed in young men with suspected AA. In postmenopausal women and older men MDCT (with or without contrast administration) is recommendable. However, in case of suspected perforation considering CRP levels more than 121.5 mg/L MDCT with administration of intravenous contrast material is essential to detect signs of AA e.g., ring-like contrast-enhancement of the thickened appendiceal wall and abscess formation in the RLQ [12,13].

On the contrary, a recent study assessed the levels of CRP/WCC in the diagnosis of AA without preoperative MDCT scan [26]. No patients with WCC/CRP both in the normal range had AA. The authors conclude that WCC and CRP were poor positive predictors of AA, both alone and in combination, and correlated poorly with the development of complications. There are several reasons for atypical clinical presentation of AA: First, the abnormal location of the appendix relative to the cecum [27]. When the inflamed appendix is located retrocecal or retroileal (11/29 cases in our study) it is shielded from the anterior peritoneal wall by the overlying cecum and ileum. Therefore, the abdominal pain seems mild to moderate and the classic shift of pain from around the navel to the RLQ may be absent. With AA in pelvic position (1/29 cases in our study), pain is often localized to the lower abdomen. Second, abdominal pain in elderly patients may be minimal and fever may not occur (5/29 cases in our study) [28]. Finally, the diagnosis of AA in pregnant women is difficult because of upward displacement of the cecum and a position of the appendix in the right subcostal area [29].

A limitation of this study is the retrospective design and the limited numbers of patients. Besides, we disregarded the clinical experience of the referring abdominal surgeon and we did not use a clinical appendicitis scoring system [30]. At same time, we did not apply enteric contrast material, because some investigators state that these did not contribute to a better diagnostic accuracy [31]. Furthermore, the patients have a longer stay in the emergency room resulting in a delay in surgical treatment. In controversy, other studies claim that enteric contrast agents reduce the number of false-negative cases, showing further findings of AA such as the arrowhead sign, the "cecal bar" sign, and focal cecal apical thickening [32].

## Conclusion

MDCT and a markedly elevated CRP level (optimal cut-off point more than 121.5 mg/L) taken together are highly accurate in the diagnosis of perforation in patients with atypical clinical presentation of AA.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Authors' contributions	MK	MA	BS	AH	SK	SV	CH	GA	JY
Research concept and design	✓	--	--	--	--	--	--	--	✓
Collection and/or assembly of data	--	--	--	✓	--	✓	--	--	--
Data analysis and interpretation	✓	--	--	--	✓	--	--	--	✓
Writing the article	✓	✓	--	--	--	--	--	--	--
Critical revision of the article	--	--	✓	--	--	--	--	✓	✓
Final approval of article	✓	--	--	--	--	--	--	--	--
Statistical analysis	--	✓	--	--	--	--	✓	--	--

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