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Inclusion of C-Reactive Protein and White Blood Cell Count in Diagnostic Workup of Patients with Clinically Suspected Appendicitis Stratifies for Imaging

R.R van Tol[1], **S.O. Breukink**[1], **M.J. Lahaye**[2] **and JPM. Derikx**[1,3*]

[1]*Department of Surgery, Maastricht University Medical Center, Maastricht, The Netherlands*

[2]*Department of Radiology, Maastricht University Medical Center, Maastricht, The Netherlands*

[3]*Pediatric surgical center of Amsterdam (Emma children hospital AMC/VUMC), Amsterdam, The Netherlands*

[*]**Corresponding author**: J.P.M. Derikx, Department of Surgery, Maastricht University Medical center, P. Debeyelaan 25, PO Box 5800, 6229 HX Maastricht, The Netherlands, Tel: +31433881494; Fax: +31433884154; E-mail: j.derikx@amc.uva.nl

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Abstract

Objectives: The aim of this retrospective study was to clarify whether plasma markers that are routinely used in the workup of patients suspected for acute appendicitis (AA) can stratify for imaging in both adults and children.

Methods: A total of 1388 patients suspected of AA between January 2008 and till 2012 were included. CRP and WBC concentrations were retrospectively abstracted from the electronic health record. Receiver operating characteristic (ROC) curves were used to assess the diagnostic accuracy for the tests and to determine the best cutoff points.

Results: In total 432 (22.4%) patients had histopathologically proven AA of whom 45 patients (10.4%) had perforated appendictis. The area under the curve (AUC 95% confidence interval [CI]) was 0.74 (95% CI = 0.70 to 0.77) for CRP and 0.74 (95% CI = 0.71 to 0.78) for WBC both in adults and children. No cut off points had high enough sensitivity and specificity to accurately diagnose (perforated) AA. However, a high sensitivity of 91% was shown at cut-off 7.5x10^9/L WBC for AA (both in adults and children). In total 244 (18%) had a cut-off < 7.5×10^9/L. Those patients could have been sent home. Only 21 (5%) patients would have been missed in the AA group and 1(0.5%) patient in the perforated appendicitis group.

Conclusions: None had clinical relevant cutoff points that could accurately discriminate between AA and other pathology, neither perforated appendicitis. However, WBC < 7.5×10^9/L for AA can identify a subgroup of 245 out of 1388 (18%) patients that could have been sent home without further imaging.

Keywords: Appendix; Symptoms early appendicitis; Abdominal pain; Inflamed appendix; Laboratory markers

Introduction

Acute appendicitis (AA) is the most common abdominal emergency requiring emergency surgery with a lifetime risk of 8.6% in males and 6.7% in females [1]. Despite its high prevalence, it remains challenging to diagnose appendicitis. The clinical presentation is often atypical and symptoms often overlap with other conditions, which results in a negative appendectomy rate of 20% [2,3]. This could lead to increased length of hospital stay, costs and higher case fatality rates. Therefore, the workup of suspected appendicitis is a prime target for improved decision making and a key recommendation of emergency surgical care guidelines. The Dutch College of Surgeons published a new national guideline in 2010 concerning the diagnostic workup of patients suspected for appendicitis, which stated that when the surgeon still suspects appendicitis after clinical and laboratory examination, the patient should proceed to imaging [4,5]. It has been reported that the negative appendectomy rate can drop to 2% if imaging is added in the workup [6]. In addition, the results of the OPTIMA trial showed that ultrasonography (US) and computed tomography (CT) improve diagnostic accuracy in patients with acute abdominal pain [7,8]. However, US only gives a good result in the hands of an experienced operator and could be hampered by fat and bowel gas that make the visualization of the appendix difficult [9]. The CT scan is compulsory, but clinicians should be reluctant to use CT because of the radiation exposure [5,10,11]. Besides, the use of imaging for every patient with acute abdominal pain will take precious time and costs in the emergency department (ED) [12].

In response to the difficulty of diagnosing appendicitis and decreasing the use of (unnecessary) imaging we need to clarify whether the laboratory markers that are routinely used in the workup of patients suspected for appendicitis can select patients for imaging. Several studies have explored the role of the classical inflammatory markers in improving the diagnosis of appendicitis [2,13,14]. These laboratory test results as white cell count (WBC) and C-reactive protein (CRP) are readily available and commonly used in patients with suspected appendicitis. In a meta-analysis of 24 studies, Andersson et al. [2] concluded that laboratory results of the inflammatory response together with clinical descriptors of peritoneal irritation and a history of migratory pain yield the most important diagnostic information. They achieve a high discriminatory power when combined [2]. Further studies show that diagnostic accuracy was better for acute appendicitis when more variables (WCC, CRP, bilirubin) were combined [15,16]. Sengupta et al. [17] even suggest

that patients with lower abdominal pain with a normal WBC and CRP can be sent home. Besides adults it can also provide a significant role supporting the clinical diagnosis of acute appendicitis in the pediatric age group [18-20]. While these markers have shown early promise, the power of the studies is limited due to the small sample size.

Still there is as yet no consensus whether WBC and/or CRP can support the clinical diagnosis of acute appendicitis. Therefore, we aim to conduct a large retrospective study to clarify whether plasma markers that are routinely used in the workup of patients suspected for appendicitis can stratify for imaging in both adults and children (2-16 years). The second objective was comparing diagnostic accuracy of these biomarkers in patients with perforated versus non-perforated appendicitis.

Methods

Study design

This is a phase 3 diagnostic study in patients suspected for appendicitis

In our country institutional review board (IRB) approval is not required for this retrospective study and patient consent was therefore waived. In our University hospital all patients are informed that their anonymized data can be used for research purposes. No patient in this study raised an objection to use his/her anonymized data.

Study setting and population

This study was conducted at the Maastricht University Medical Center (MUMC). We identified our patient population from an already existing database [5]. A researcher (EM) searched the electronic patient databases of MUMC for all patients presenting at the emergency department and seen by the surgeon with a suspected acute appendicitis in the differential diagnosis between January 1st 2008 till December 31st 2012. One group was included before the Dutch guideline implementation (2008-2009) and another group after the Dutch guideline implementation (2011-2012). Patients from the transition period (2010) were not included. A researcher (RT) retrospectively reviewed the medical chart for the final diagnosis, histological outcome and lab results.

Inclusion criteria were referral by a general practitioner with the suspicion of appendicitis or patients presenting at the emergency department or outpatient clinic with acute pain in the right lower abdomen. Exclusion criteria were clear alternative clinical diagnosis (e.g. cholecystitis), recent abdominal trauma, and previous appendectomy (which was unknown at the time of patient referral) [5]. We also excluded 174 patients because blood test results were not available.

Study protocol

The patients after implantation of the guideline were evaluated following a standard diagnostic procedure described in the national guideline proposed by the Dutch College of Surgeons in 2010. The group patients before the guideline implantation in 2010 were already evaluated according to the guideline in Maastricht.

This included history, physical examination, routine CRP and WBC laboratory tests and imaging of the abdomen by performing US or CT. In this guideline US is recommended as the first choice imaging technique in patients with suspected appendicitis. In case of negative or inconclusive US, the patient proceeds to additional CT examination. A patient only underwent surgery after imaging of the abdomen [5,7]. A laparoscopic appendectomy is the standard surgical approach. An 'open' appendectomy was only performed when there were complications during the laparoscopic procedure.

In case of very low clinical suspicion of appendicitis the patient was seen next day at the outpatient clinic and reassessed.

Plasma measurements

EDTA plasma samples were collected on admission to the emergency department (ED). These samples were centrifuged after collection for 12 minutes at 2100 rpm and cooled down to 5 degrees until analysis. The laboratory personal was unaware of the final diagnosis. CRP and WBC concentrations were determined in standard fashion by the laboratory of clinical chemistry and hematology.

The golden standard for diagnosing appendicitis is histopathological examination. Appendicitis was histologically demonstrated by infiltration of the mucosa of the appendix by neutrophil granulocytes, with or without local peritonitis. Based on review of the postoperative report, the diagnosis of (perforated) appendicitis is made. Diagnoses other than appendicitis were categorized as other acute abdominal pathology, nonacute abdominal pathology and urologic/gynecologic pathology.

Statistics

All statistical analyses were performed with GraphPad Prism for windows (GraphPad Software Inc, San Diego, CA) and SPSS 17.0 for Windows (IBM SPSS, Armonk, NY). A p-value of <0.05 was considered statistically significant. Normality was tested using Kolmogorov-Smirnov test. A two-tailed Mann-Whitney U test was used to compare CRP, WBC between the group with acute appendicitis and the other diagnoses.

To study the diagnostic accuracy of the markers in patients with appendicitis, receiver operating characteristic (ROC) curves were used. The area under the curve (AUC) of the ROC gives a percentage of the times that a random patient from the group with the disease is actually detected by the test in question [21], with an AUC of 0.5 indicating no discriminatory ability and an AUC of 1.0 indicating maximal discriminatory ability [22]. The ideal cut off points are assessed as maximum of sum of sensitivity and specificity.

The diagnostic value of CRP and WBC was predicted with sensitivity, specificity and likelihood ratios. Sensitivity, specificity and likelihood ratios varied when different cut-off values were examined (sensitivity analysis).

With a multivariable logistic regression model the combined diagnostic value of the variable markers are studied [23]. We followed the guidelines for accurate logistic regression modeling. The continuous variables were checked for the absence of influential multi-collinearity, lack of strongly influential outlier values, and the assumption of linearity in the logit. The markers (CRP and WBC) were entered as continuous variables and the presence of appendicitis as a categorical dependent variable (patients with appendicitis were coded 1, and other diagnoses were coded with 0). The predictive probabilities were calculated and the diagnostic accuracy was determined using ROC curves to calculate the AUCs.

Results

Characteristics of study subjects

Baseline patient characteristics of 1388 patients suspected for appendicitis are presented in Table 1.

Of the 1388 patients 341 were children. Baseline patient characteristics are shown in Table 2.

	Appendicitis	**Other Diagnoses**
N	432 (out of 1388)	956 (out of 1388)
Age, yr (range)	34.8 (3-89)	30.2 (2-89)
Sex (M:F)	229: 203	327: 629
Operated	432	24 appendix sana
Diagnosis	Nonperforated appendicitis (n = 387)	Nonacute abdominal pathology (n = 725)
	Perforated appendicitis (n = 45)	Gastroenteritis (n = 80)
		Irritable bowel syndrome (n = 12)
		Constipation (n = 84)
		Aspecific abdominal pain (n = 549)
		Other acute abdominal pathology (n = 124)
		Hier ook puntje voor Diverticulitis (n = 32)
		En hier ook puntje voor Crohn (n = 4)
		Cholecystolithiasis (n = 12)
		Pneumonia (n = 27)
		Tendinomyalgia (n = 8)
		Ileus (n = 16)
		Colitis (n = 5)
		Aneurysm (welk?) (n = 1)
		Mesentiric lymphadenitis (N = 19)
		Urologic and gynecologic pathology (n = 107)
		Adnexitis (n = 5)
		Urolithiasis (n = 22)
		Pelvic Inflammatory Disease (n = 2)
		Ovarian tumor (n = 3)
		Urinary tract infection (n = 45)
		Ovulation bleeding (n = 7)
		Ovarian cyst (n = 7)
		Adnexal torsion (n = 2)
		Pyelonefritis (n = 7)
		Endometriosis (n = 2) Gravitas (n = 5)

Table 1: Patient and disease characteristics.

	Appendicitis	Other Diagnoses
N	91 (out of 341)	250 (out of 341)
Age, yr (range)	10.7 (2-16)	11.5 (2-16)
Operated	91	3 appendix sana
Diagnosis	Nonperforated appendicitis (n = 72)	Nonacute abdominal pathology (n = 209)
	Perforated appendicitis (n = 19)	Gastroenteritis (n = 15)
		Irritable bowel syndrome (n = 1)
		Constipation (n = 30)
		Mesenteric lymphadenitis (n = 19)
		Aspecific abdominal pain (n = 144)
		Other acute abdominal pathology (n = 24)
		Pneumonia (n = 24)
		Urologic and gynecologic pathology (n = 17)
		Urinary tract infection (n = 13)
		Ovulation bleeding (n = 3)
		Pyelonephritis (n = 1)

Table 2: Patient and disease characteristics for children (2-16 years).

Plasma levels of CRP and WBC in patients with suspected AA

First, the median WBC and CRP were derived for the groups: appendicitis versus other diagnoses (in both adults and children) and perforated appendicitis versus nonperforated appendicitis. The median plasma concentrations of CRP and WBC were significantly higher in the 432 patients with AA than in the 956 patients with other diagnoses (CRP: 87.8 [1.0 to 532] mg/L vs 32.8 [1.0-486] mg/L; WBC: 14.1×10^9 [4.0 to 43×10^9] L vs. 9.9×10^9 [2 to 48×10^9] L; $p < 0.001$). For children we found the same: (CRP: 47 [1.0 to 247] mg/L vs. 20.2 [1.0 to 447] mg/L; WBC: 15.8×10^9 [5 to 43×10^9] L vs 9.8×10^9 [2.0 to 48×10^9] L; $p < 0.001$).

The median plasma concentrations of CRP and WBC were also significantly higher in patients with perforated appendicitis than in patients with non-perforated appendicitis (CRP: 154 [1.0 to 458] mg/L, vs. 81.4 [1.0 to 532] mg/L, p 0.001; WBC: 17.0×10^9 [9 to 43×10^9] L, vs. 13.8×10^9 [4 to 31×10^9] L; $p < 0.033$).

ROC curves of CRP and WBC in patients with suspected AA

The clinical usefulness of plasma markers for early diagnosis of AA depends largely on cutoff points that most accurately discriminate between patients with AA and those without. Therefore ROC curves were calculated and the ideal cutoff points were assessed as the maximum sum of sensitivity and specificity of the markers. Sensitivity and specificity values may vary when different cut-off points are taken.

The areas under the curve with 95% confidence intervals (CI) for CRP and WBC were 0.73 (95% CI = 0.70 -0.77) and 0.74 (95% CI = 0.71-0.78) in the appendicitis group. The areas under the curve for CRP and WBC in children were 0.74 (95% CI = 0.68-0.81) and 0.79 (95% CI = 0.73-0.86).

In the perforated appendicitis group the areas under the curve showed worse discriminatory power; the AUC for CRP and WBC were 0.69 (95% CI = 0.58-0.80) and 0.63 (95% CI = 0.52-0.73) in the perforated appendicitis group.

The optimum cutoff points, sensitivity, specificity, likelihood ratio and AUC are shown in (Table 3). The results show that the cutoff points for the ROC that yield the best combination of sensitivity and specificity lead to poor discrimination. A cut-off point with maximum sensitivity is considered most useful because you don't want to miss the diagnosis AA. All cutoff points with the highest sensitivity are presented in (Table 4).

Histology	Variable	Cut off Point	Sensitivity	Specificity	LR+	LR-	ROC AUC	P-value
			(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	
AA	CRP	18.5 mg/L	68(62-7)	67 (64-70)	2.07(1.85-2.31)	0.48(0.41-0.55)	0.73 (0.70-0.77)	<0.001
	WCC	11.5×10^9/L	68 (63-73)	70 (67-73)	2.27(2.02-2.55)	0.46(0.40-0.53)	0.74 (0.71-0.78)	<0.001
AA in Children	CRP	9.5 mg/L	71 (58-82)	68 (61-74)	2.21(1.79-2.74)	0.42(0.33-0.55)	0.74 (0.68-0.81)	<0.001
	WCC	11.5×10^9/L	76 (64-86)	71 (65-77)	2.62(2.10-3.27)	0.34(0.25-0.45)	0.79 (0.73-0.86)	<0.001
PA	CRP	73.5 mg/L	65 (44-83)	65 (59-71)	1.85(1.43-2.39)	0.55(0.37-0.81)	0.69 (0.58-0.80)	0.001
	WCC	13.5×10^9/L	65 (44-83)	51 (45-57)	1.31(1.03-1.67)	0.70(0.47-1.05)	0.63 (0.52-0.73)	0.033

Table 3: The levels of C-reactive protein (CRP) and white cell count (WCC) corresponding to optimal sensitivity and specificity for either acute appendicitis (AA), acute appendicitis in children and perforated appendicitis (PA).

Histology	Variable	Cutoff Point	Optimal sensitivity	Optimal specificity	LR+	LR-	P-value

AA	CRP	4.5 mg/L	86 (82-9)	44 (41-48)	1.54 (1.44-1.64)	0.32(0.25-0.40)	<0.001
	WBC	7.5×10^9/L	91 (87-94)	31 (28-34)	1.32 (1.25-1.39)	0.29(0.21-0.40)	<0.001
AA in Children	CRP	3.5 mg/L	85 (73-93)	56 (49-63)	1.93 (1.64-2.27)	0.26(0.18-0.39)	<0.001
	WBC	7.5×10^9/L	91 (91-99)	18 (13-24)	1.11 (1.02-1.20)	0.52(0.29-0.90)	<0.001
PA	CRP	11.5 mg/L	92 (75-99)	26 (21-32)	1.23 (1.11-1.37)	0.34(0.13-0.88)	0.0991
	WBC	9.5×10^9/L	96 (80-99)	21 (16-26)	1.21 (1.11-1.31)	0.21(0.05-0.83)	<0.001

Table 4: The levels of C-reactive protein (CRP) and white cell count (WCC) corresponding by the maximum sensitivity for either acute appendicitis (AA), acute appendicitis in children and perforated appendicitis (PA).

A high sensitivity of 91% was shown at cut-off 7.5×10^9/L WBC for AA in both adults and children. High sensitivity of 96% was shown at cut-off 9.5×10^9/L for PA group.

Using this cut-off in our patient population, 245 patients could have been sent home without further imaging, a reduction of 18% [21]. (5%) patients would have been missed in the AA group and 1 (2%) patient in the perforated appendicitis group. Using a WBC $<7.5\times10^9$/L 77 out of 341 children (23%) could have been sent home without further imaging [5]. 1.7% children would have been missed with acute appendicitis and none with perforated appendicitis.

Combining the Markers CRP and WBC

Because no single marker accurately differentiated between patients with AA and patients with other diagnoses we combined the various tests using a multivariable logistic regression model. Combining CRP with WBC results in an AUC of 0.53 (95% Cl: 0.49-0.56). Unfortunately, AUC values for the combination of the markers were not significantly better than the highest AUC value of the single markers.

Discussion

In this study we investigated the diagnostic accuracy of CRP and WBC for patients with suspected AA among a large population. This retrospective study shows that patients presenting at the ED with a WBC $<7.5\times10^9$/L in combination with low clinical suspicion for AA may be sent home safely without the need of further imaging. It can stratify a subgroup of 245 patients (18%) without missing many patients with AA or perforated appendicitis. These low-risk patients could be discharged with appropriate safe netting. Pediatric patients with a WBC $<7.5\times10^9$/L and low clinical suspicion could also be sent home, potentially leading to a reduction of imaging in 23% of the patients.

The debate about the benefit of laboratory tests in diagnosing appendicitis still continues. Many researchers have already investigated the potential role of the plasma markers WBC and CRP. These markers contribute to the diagnosis of appendicitis, but they are also unable to change the diagnostic management of suspected appendicitis on their own. Therefore imaging still plays a pivotal role in the diagnosis AA. The use of preoperative imaging in the workup of patients with suspected appendicitis leads to low negative appendectomy rates of 1.7% [24]. However, using imaging for every patient with acute abdominal complaints is time-consuming at the ED and leads to unnecessary exposure to radiation in case of using CT [25]. Reducing the use of imaging for patients with acute abdominal pain would be beneficial.

Therefore, we identified a new role for laboratory tests in patients with suspected AA. It should not be used for diagnostic purposes, as is already shown previously. Our results are in line with these reports, showing that there is a significant difference in plasma CRP and WBC levels between patients with (perforated) appendicitis and other abdominal complaints. However, the determined cutoff points using ROC curves led to poor discrimination between patients with appendicitis and other diagnoses, which make these tests not clinically useful for diagnostic purposes. Unfortunately, AUC values for the combination of markers were not better than the highest AUC value of the single markers.

Therefore, we find an important role for WBC in stratifying which patients with suspected AA should undergo imaging. We considered a cutoff point that represented maximum sensitivity as the best to differentiate between patients with and without appendicitis. When a test has high sensitivity, a negative result effectively rules out the diagnosis [26]. When this principle was applied, the sensitivity of WBC with a cutoff point of 7.5×10^9/L for AA was 91% for both adults and children. For the perforated appendicitis group we found a sensitivity of 96% with a cut-off point of 9.5×10^9/L.

Our data showed that WBC had sensitivity equivalent or better than CRP. Therefore WBC would be the preferred biomarker for patients suspected for appendicitis to stratify for imaging. Besides, CRP is quite limited for appendicitis in general [27]. One study even reported that the CRP level was within normal limits in some AA cases. A possible explanation is that CRP level starts to increase 12-24 hours after the symptom onset. WBC count manifest after 5-24 hours.

The degree of WBC elevation has been extensively studied. It is commonly elevated in patients with acute appendicitis. Because there is a great variability in the WBC-concentration cutoffs, it is difficult drawing precise conclusions. A meta-analysis in 2003 gives a representative approximation of the true sensitivity (83%) and specificity (67%) of WBC $>10\times10^9$/L with a positive and negative likelihood ratio of 2.52 and 0.26. Their conclusion is that a WBC $>10\times10^9$/L only alter the probability of the diagnosis to a modest degree [2] calculated a sensitivity and a specificity of 100% when either CRP >10 mg/L or WBC $>11\times10^9$/L. A study in 2007 among children shows that a cutoff point $<10\times10^9$/L decreases the likelihood of appendicitis [28]. Another study showed that WBC $<7.5\times10^9$/L can identify a subgroup of patients that may be sent home without further evaluation [29]. A similar study even showed that a WBC level above 12×10^9/L was allowed to diagnose AA [30].

Today there is discussion about treating uncomplicated (nonperforated) AA with antibiotic therapy instead of surgery. The APPAC Trial is the largest multicenter randomized clinical trial comparing antibiotic therapy with appendectomy for the treatment of acute appendicitis. In the study they found that patients with uncomplicated appendicitis 73% did not require appendectomy within 1 year of initial presentation [31]. So in the future surgeons need to distinguish patients who are candidates for antibiotic therapy from those who are not. in this light measurement of plasma levels of WBC could be helpful for the identification of patients with uncomplicated AA. Also for the daily evaluation of treatment with antibiotics laboratory results could play an important role.

There are some limitations that must be considered when evaluating the results. First, the time between the start of the abdominal complaints and presentation at the ED was not recorded. This might be important since the diagnostic value of biomarkers is time-dependent [29].

The second limitation related to the design of our study, is that in non-operated patients the diagnosis of non-specific abdominal pain could not be made with certainty. However, our patients are able to get proximate follow-up. That allows us to reevaluate discharged patients the following day.

Third, it is worthwhile to mention the fact that the Dutch system relies on patients being referred to the ED by their GPs. Thus physicians have already screened the patients what may alter the incidence of acute appendicitis in our population.

Finally, we did not collect information for AA-scores (e.g. Alvarado), since we and others earlier reported that these are not useful for daily clinical practice [10,15,22,29-31].

Conclusion

In conclusion, this phase III diagnostic study shows that both CRP and WBC didn't have high enough sensitivity and specificity to be clinically useful for suspected appendicitis. However, it is possible to stratify patients for imaging by the plasma markers CRP and WBC and in that way reduce requirement for abdominal imaging. A WBC of $<7.5\times10^9$/L has a high sensitivity of 91% and in combination with low clinical suspicion for acute appendicitis, it can stratify a subgroup of 245 patients (18%) that may be sent home without further imaging with appropriate safe-netting. A WBC $<7.5\times10^9$/L for AA in children would have led to 23% of the children sent home without further imaging. A WBC $>7.5\times10^9$/L selects patients in whom imaging should be considered to localize the inflammatory process. A WBC $<9.5\times10^9$/L with a sensitivity of 96% can stratify patients to distinguish between AA and perforated appendicitis.

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