

Diagnostic value of laboratory parameters for complicated appendicitis: A two-center study

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Abstract. There are two types of treatment for acute appendicitis (AA): surgery and antibiotic therapy. Some patients with complex appendicitis are treated with surgery; however, for uncomplex appendicitis, most could be treated effectively with antibiotics instead. How to distinguish complex appendicitis from uncomplex appendicitis before surgery is currently unknown. The present study aimed to assess the efficacy of the laboratory parameters to diagnose complicated appendicitis. Data from 1,514 cases with acute appendicitis who were admitted to Beijing Tsinghua Changgung Hospital and Beijing Aerospace General Hospital (both Beijing, China) from January 2016 to September 2021 were retrospectively analyzed. All cases were divided into uncomplicated and complicated appendicitis. Independent variables were analyzed by uni- and multivariate logistic regression analyses. Receiver operating characteristic (ROC) curve analysis was used to identify significant parameters in the multivariate logistic regression analysis. Cut-off values, sensitivity, specificity and accuracy with area under the curve (AUC) > 0.600 were considered significant parameters. Significant differences were found in age ($P < 0.001$), body temperature ($P < 0.001$), white blood cell (WBC) count ($P < 0.001$), C-reactive protein (CRP; $P < 0.001$), neutrophil count ($P < 0.001$), neutrophil-to-lymphocyte ratio (NLR, $P = 0.019$), platelet-to-lymphocyte ratio (PLR, $P < 0.001$), platelet count ($P < 0.001$), coefficient of variation (CV) and standard deviation (SD) of red blood cell distribution width (RDW); both $P < 0.001$, mean platelet volume (MPV, $P < 0.001$)

and total ($P < 0.001$) and direct bilirubin ($P < 0.001$) between the two groups. CRP, neutrophil count, NLR, PLR, platelet count, RDW-CV, RDW-SD, MPV and direct bilirubin levels were found as the independent variables to diagnose complicated appendicitis. In patients with acute appendicitis, CRP > 22.95 mg/l, NLR > 5.7, serum direct bilirubin > 6.1 mmol/l and RDW-SD > 17.7 fl were significantly associated with complicated appendicitis.

Introduction

Acute appendicitis is a frequently encountered acute abdominal condition, with a morbidity rate of 1.5-1.9 per 10 million (1,2). Its incidence is 1.4 times higher in men compared with that in women (1). Lifetime risk of experiencing acute appendicitis is 7-8% (1). Elderly patients have higher incidence of complicated appendicitis, reported rates of perforation and morbidity were as high as 70 and 48%, respectively (3). Notably, 17-30% of patients with acute appendicitis may exhibit appendiceal perforation; this occurrence is notably more prevalent in the elderly (1,2). Appendicitis is divided into uncomplicated and complicated appendicitis according to its pathology (4). Uncomplicated appendicitis has a mild infection and fewer complications and can be treated with antibiotics (5). On the other hand, surgery is the primary treatment for complicated appendicitis (5). Early diagnosis and management are crucial to decrease incidence of complications and the length of hospitalization (4,5).

Several diagnostic modalities are available for appendicitis, such as laboratory inflammatory markers, scoring systems and imaging methods (6,7). Only 60% of patients present with typical symptoms, including shifting right lower abdominal pain, fever, nausea, and vomiting (1,2,8). The frequently measured laboratory parameters are C-reactive protein (CRP), white blood cell (WBC) count and neutrophil percentage. However, these tests can only evaluate the presence of abdominal infection and severity (1,7,9,10). Abdominal ultrasound and computed tomography (CT) scan are used in the diagnosis of appendicitis. Sensitivity and specificity of ultrasound are 86 and 81%, respectively, due to the influence of the intestinal gas (4,11). Although non-contrast-enhanced CT has better sensitivity and specificity (92.3%) than ultrasound (81%) (1,12,13), the high cost and the risk of radiation

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may limit its broad application. Therefore, evaluation of acute appendicitis based on laboratory tests is essential.

Over the past decade, studies have reported that neutrophil count and percentage, neutrophil-to-lymphocyte ratio (NLR), platelet (PLT) count, mean platelet volume (MPV) and direct bilirubin are key parameters in the diagnosis of appendicitis and predicting the complications (1,14-19). A recent study demonstrated an association between plasma sodium concentration ≤ 135 mmol/l and perforated appendicitis (5). The present study aimed to evaluate the diagnostic value of CRP, WBC count, NLR, PLT, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), red blood cell distribution width (RDW), MPV and serum bilirubin levels for acute appendicitis. The present study aimed to propose a standard was for the management of acute appendicitis.

Materials and methods

Study design and participant selection. The present study was approved by the Institutional Review Board of Beijing Tsinghua Changgung Hospital (Beijing, China; approval no. 22029-1-01). Because of the retrospective nature of the study, the requirement for patient consent for inclusion was waived. Data from 1,514 cases with acute appendicitis who were admitted to the Gastrointestinal Department of Beijing Tsinghua Changgung Hospital ($n=978$; 64.6%) and Surgery Department of Beijing Aerospace General Hospital (Beijing, China; $n=536$; 35.4%) from January 2016 to September 2021 were retrospectively analyzed. The inclusion criteria were as follows: i) Age ≥ 14 years and ii) pathological confirmation of acute appendicitis. The exclusion criteria were as follows: i) Postoperative pathology indicating a normal appendix; ii) concurrent autoimmune or infectious diseases of non-appendiceal origin; iii) concurrent severe liver, cardiovascular or kidney diseases; iv) concurrent cancer or other blood related diseases and v) antibiotic treatment <12 h before the surgery and blood test.

Blood test was performed <12 h before the surgery. Flow cytometry was used to detect blood cell composition and hydraulic focusing method (Automated Hematology Systems XN, Automated Hematology Analyzer XN series XN master, flow cell count + DNA/RNA fluorescence staining) was used for the complete blood count and blood chemistry tests. Additionally, liver function test was conducted using diazonium salt method (BECKMAN COULTER CHEMISTRY ANALYZER AU5800 Serie, Beckman Coulter AU5800 software, B000017AA, Beckman Coulter). All the cases underwent laparoscopic appendectomy.

Appendix pathology was evaluated by an experienced pathologist from each hospital. The pathological results were classified as follows: Simple/phlegmonous (intraoperative signs of congestion, an increased diameter, red) color change, exudate or pus; or histopathologic signs of transmural inflammation, ulceration, or thrombosis, with or without extramural pus), gangrenous and perforated (perioperative signs of a friable appendix with purple, green or black color changes, a visible perforation, and/or abscess formation, or histopathologic signs of transmural inflammation with signs of necrosis or perforation) appendicitis (20). Subsequently, all cases were categorized into two groups: Uncomplicated,

comprising simple and phlegmonous appendicitis, and complicated appendicitis, encompassing gangrenous and perforated appendicitis and periappendicular abscess.

Data collection. The information of age, sex and body temperature was retrieved from the medical records. Routine blood tests provided data on WCC, CRP, MPV, neutrophil count and percentage, platelet (PLT), lymphocyte count and coefficient of variation (CV) and standard deviation (SD) of RDW. Liver function test yielded values for total and direct bilirubin and CRP. NLR was calculated as the ratio of neutrophil count to lymphocyte count, LMR as the ratio of lymphocyte count to monocyte count and PLR as the ratio of platelet count to lymphocyte count.

The primary outcomes of the study included the values of WCC, CRP, MPV, neutrophil count and percentage, lymphocyte count, RDW-CV and RDW-SD. The secondary outcomes were values of total and direct bilirubin, CRP, NLR, LMR and PLR.

Statistical analysis. The statistical analysis was performed using SPSS 25.0 software (IBM Corp.). Normally distributed continuous variables are expressed as mean \pm SD and compared using unpaired t test. Abnormally distributed continuous variables are presented as median and compared using the Kruskal-Wallis H test. Numerical data were expressed as number and percentage and compared using χ^2 test. Multivariate logistic regression analysis was conducted on parameters exhibiting significant differences in the univariate analysis. Diagnostic accuracy was evaluated by receiver operating characteristic (ROC) curve analysis. The appropriate cut-off values were identified and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated for parameters with an area under the curve (AUC) >0.600 . All tests were two-sided. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The cohort comprised 780 (51.5%) men and 734 (48.5%) women with a mean age of 36.000 ± 15.135 (range, 14-88) years. A total of 1,172 (77.4%) cases were allocated to the uncomplicated appendicitis group, while 342 (22.6%) cases were in the complicated appendicitis group. Age, body temperature, WCC, CRP, neutrophil percentage and count, NLR, PLR, PLT, RDW-CV, RDW-SD, MPV, total bilirubin and direct bilirubin exhibited significant differences (all $P<0.001$) between the two groups as evidenced by univariate analysis (Table I).

Multivariate logistic regression analysis revealed that CRP ($P<0.001$), neutrophil count ($P<0.001$), NLR ($P=0.019$), PLR ($P<0.001$), PLT ($P<0.001$), RDW-CV ($P=0.045$), RDW-SD ($P<0.001$), MPV ($P=0.007$) and direct bilirubin ($P<0.001$) were the independent risk factors associated with complicated appendicitis (Table II). According to ROC curve analysis, factors with AUC >0.600 were CRP, NLR, RDW-SD and direct bilirubin (all $P<0.001$; Table II). The cut-off values of CRP, NLR, RDW-SD and direct bilirubin are presented in Table III.

Table I. Univariate analysis.

Variable	Uncomplicated appendicitis	Complicated appendicitis	P-value
N	1,172	342	
Median age (range), years	35 (14-81)	41 (16-88)	<0.001
Sex (%)			0.868
Male	606 (51.70)	174 (50.90)	
Female	566 (48.30)	168 (49.10)	
Mean body temperature, °C	37.0±0.70	37.50±0.93	<0.001
Mean WBC count, x10 ⁹ /l	13.0±3.92	14.24±3.98	<0.001
Mean CRP, mg/l	10.18±50.8	43.29±74.41	<0.001
Mean neutrophil, %	84.40±9.40	86.20±7.73	<0.001
Mean neutrophil count, x10 ⁹ /l	10.79±3.93	12.17±3.67	<0.001
Mean NLR	8.21±8.36	9.95±11.88	<0.001
Mean LMR	2.43±3.12	1.87±3.43	0.919
Mean PLR‡	167.53±200.27	191.43±374.31	<0.001
Mean PLT, x10 ⁹ /l	222.50±57.46	225.50±58.21	<0.001
Mean RDW-CV, %	11.90±1.55	12.10±1.36	<0.0001
Mean RDW-SD, fl	37.40±12.6	38.50±10.56	<0.001
MPV, fl	10.30±14.28	10.10±11.80	<0.001
Mean bilirubin, mmol/l	14.60±8.78	17.95±10.78	<0.001
Mean direct bilirubin, mmol/l	4.24±2.6	5.80±3.80	<0.001

WBC, white blood cell; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; RDW, red blood cell distribution width; MPV, mean platelet volume; CV, coefficient of variation.

Table II. Logistic regression and ROC curve in factors associated with complicated appendicitis.

Variable	Multivariate analysis			ROC curve analysis		
	OR	95% CI	P-value	AUC	95% CI	P-value
CRP	1.008	1.005-1.010	<0.001	0.679	0.642-0.714	<0.001
Neutrophil count	1.120	1.055-1.189	<0.001	0.589	0.556-0.621	<0.001
NLR	0.944	0.900-0.991	0.019	0.603	0.556-0.621	<0.001
PLR	1.005	1.003-1.008	<0.001	0.573	0.537-0.607	<0.001
PLT	0.996	0.993-1.000	0.039	0.502	0.466-0.535	<0.001
RDW-CV	0.809	0.657-0.996	0.045	0.579	0.544-0.610	<0.001
RDW-SD	1.147	1.079-1.219	<0.001	0.605	0.571-0.637	<0.001
MPV	1.067	1.018-1.118	0.007	0.567	0.535-0.601	<0.001
Direct bilirubin	1.128	1.075-1.184	<0.001	0.657	0.622-0.690	<0.001

OR, odds ratio; AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; RDW, red blood cell distribution width; MPV, mean platelet volume; CV, coefficient of variation.

Discussion

Acute appendicitis is the prevailing cause of acute abdominal conditions, with morbidity rates up to 2% (1,21). The diagnosis of appendicitis depends on symptoms, signs, laboratory tests and imaging results (1,7,8). Surgery is the primary therapy for acute appendicitis, especially for complicated appendicitis (22-25). Complicated appendicitis accounts for 18-34% of acute appendicitis cases (1). Conservative treatment is the first

option for uncomplicated appendicitis (1,7,8,26). Therefore, it is necessary to choose an effective and simple method to distinguish complicated and uncomplicated appendicitis. Parameters such as temperature, CRP, WBC, NLR, PLR, MPV, RDW-CV, RDW-SD and total bilirubin may improve the diagnostic accuracy for complicated appendicitis, however, the efficacy varies (10,16-19,21,27-29). The present study analyzed 1,514 cases who underwent laparoscopic appendectomy at two surgical centers. The results suggested that CRP, neutrophil,

Table III. Proposed cut-off values for significant parameters in prediction of acute complicated appendicitis.

Variable	Cut-off value	Sensitivity, %	Specificity, %	PPV	NPV	pLLR	nLLR	AUC
CRP	22.95	64.24	66.09	38.10	85.00	1.89	0.54	0.679
NLR	5.7	82.46	32.51	26.30	86.40	1.22	0.54	0.603
RDW-SD	17.7	82.16	33.45	26.50	86.50	1.23	0.53	0.605
Direct bilirubin	6.1	47.66	78.16	38.90	83.70	2.18	0.67	0.657

PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; pLLR, positive likelihood ratio; nLLR, negative likelihood ratio; AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; RDW, red blood cell distribution width.

NLR, PLR, PLT, RDW-CV, RDW-SD, MPV and direct bilirubin could be the independent risk factors of complicated appendicitis.

CRP is a serum inflammatory marker and a critical factor associated with complicated appendicitis (16,19,30). Its concentration increases rapidly by several-fold in the early stage of inflammation (6-12 h) (31). Notably, WBC count is a sensitive indicator during the first 24 h of acute appendicitis, while CRP is sensitive after the first 24 h (31). Ahmed (32) reported that the probability of appendix perforation significantly increases when CRP >48 mg/dl. A study including 42 acute appendicitis cases found that the sensitivity and specificity of perforated appendicitis are 71 and 100%, respectively, when CRP is >40.1 mg/dl (33). Choudhary *et al* (34) demonstrated that the sensitivity and specificity of perforated appendicitis are 100 and 54%, respectively, when CRP is >6.15 mg/l. Hence, the appropriate cut-off of CRP is key for distinguishing complicated appendicitis. The present study found that the sensitivity and specificity of complicated appendicitis were 64.24 and 66.09%, respectively, when CRP was >22.95 mg/l. This cut-off value was lower than that reported in previous studies (32,33).

NLR is obtained from complete blood count. It is a routine and cost-effective blood test during diagnosis of appendicitis. NLR can effectively elucidate the severity of acute appendicitis (18,27,28,35,36), while the cut-off value remains controversial (27,28,35,36). Ishizuka *et al* (14) reported that NLR of 8.0 is significantly associated with gangrenous appendicitis based on the analysis of 314 cases who underwent appendectomy. Kahraman *et al* (15) analyzed 897 cases and concluded that NLR of 5.74 is associated with complicated appendicitis; sensitivity and specificity of clinical features were 70.8 and 48.5%, respectively. The present study reported an NLR of 5.7 associated with complicated appendicitis and the sensitivity and specificity were 82.46 and 32.51%, respectively. This finding was similar to that of Kahraman *et al* (15) and lower than that reported by Ishizuka *et al* (14). Prior research (14) suggests that the lower the cut-off value of NLR, the higher the sensitivity of NLR. Cut-off value of 3.5 results in the highest sensitivity (35) and the specificity increases when NLR >5.0 (21). Further investigation with a larger sample size is essential to find an optimal cut-off value of NLR.

The serum bilirubin levels increase due to liver dysfunction during infection, especially sepsis. Hence, serum bilirubin levels are included in the evaluation of patients

with complicated appendicitis (37-39). The sensitivity and specificity of total and direct bilirubin in recognizing complicated appendicitis are 48 and 61%, respectively (40). Sand *et al* (41) reported that hyperbilirubinemia has a specificity of 86% for appendiceal perforation or gangrene, while CRP has a specificity of 35%. Estrada *et al* (42) found that bilirubin levels >1 mg/dl are associated with three-fold risk of perforated appendicitis. Pogorelić *et al* (43) demonstrated that hyperbilirubinemia is a reliable indicator for perforated acute appendicitis in children with sensitivity of 92% and specificity of 77.3%. By contrast, certain studies have reported no diagnostic value for bilirubin in the prediction of perforated appendicitis (44,45). Bilirubin alone is sufficient to identify patients with acute appendicitis and predict perforated appendicitis. The value of bilirubin as a marker increases when combined with clinical symptoms and other blood markers (44,46). In the present study, total and direct bilirubin levels were significantly elevated in the complicated appendicitis group. Direct bilirubin was an independent risk factor of complicated appendicitis with a sensitivity of 47.66% and specificity of 78.16% when the cut-off value was 6.1 mmol/l. Although total bilirubin levels can be measured, few studies have reported the efficiency of direct bilirubin (44-46). Therefore, these results need to be verified with further studies.

RDW reflects volumetric heterogeneity of red blood cells. At present, it is primarily used for the differential diagnosis of anemia (47,48). RDW is altered in certain types of inflammatory and infectious disease, such as inflammatory bowel disease, celiac disease, acute pancreatitis, rheumatoid arthritis, bacteremia, sepsis and septic shock (47-51). Previous studies have reported a strong correlation between RDW and inflammatory markers, such as CRP, erythrocyte sedimentation rate and interleukin-6 (48,49). The inflammatory mediators affect survival of red blood cells in the circulation by suppressing erythrocyte maturation. Thus, newer, larger reticulocytes enter peripheral circulation and increase the RDW (48). Narci *et al* (52) found that RDW significantly decreases in patients with acute appendicitis compared with healthy individuals. Conversely, Aktimur *et al* (53) and Tanrikulu *et al* (54) did not identify any diagnostic value of RDW in acute appendicitis. Jung *et al* (55) demonstrated that the RDW is significantly higher in complicated appendicitis compared with that in the uncomplicated appendicitis; by contrast, RDW does not significantly differ between patients with appendicitis

and healthy individuals. A recent meta-analysis, which included 5,222 cases, showed that RDW does not differentiate patients with acute appendicitis from healthy individuals (56) and highlighted the lack of evidence for the diagnosis of acute appendicitis using RDW. The results of the present study indicated that RDW-CV and RDW-SD were independent risk factors for complicated appendicitis. RDW-SD had a sensitivity of 82.16% and specificity of 33.45% for complicated appendicitis when the cut-off value was 17.7 fl. Therefore, RDW could serve as a parameter to identify complicated appendicitis.

Although the present multicenter study indicated CRP, NLR, direct bilirubin and RDW-SD as potential biomarkers for complicated appendicitis, the retrospective nature of the analysis may introduce the possibility of bias. Therefore, randomized controlled trials should be conducted. Moreover, the present study only assessed laboratory results. In the future, physical examination should also be included to improve sensitivity and specificity.

In conclusion, elevated levels of CRP (>22.95 mg/l), NLR (>5.7), RDW-SD (>17.7 fl) and direct bilirubin (>6.1 mmol/l) could serve as valuable indicators for diagnosing acute complicated appendicitis. For patients exhibiting these indicators, surgery is the primary recommended treatment.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

QZ, HWZ and WQL designed the study, analyzed data and wrote the manuscript. FW and PZ reviewed the manuscript and analyzed and interpreted data. QZ, HWZ, and WQL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Beijing Tsinghua Changgung Hospital (Beijing, China approval no. 22029-1-01). The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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