Diagnostic Value of Laboratory Parameters for Complicated Appendicitis: A Two-center Study

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Research Article

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Abstract

BACKGROUND

The present study aimed to examine the efficacy of the laboratory parameters with respect to complicated appendicitis.

METHODS

A total of 1514 cases with acute appendicitis at the Beijing Tsinghua Changgung Hospital and Aerospace Center Hospital from January 2016 to September 2021 were reviewed in this retrospective study. All cases were divided into uncomplicated and complicated appendicitis groups according to the appendix pathology. The efficacy of the laboratory parameters was evaluated in recognition of complicated appendicitis. Independent variables were analyzed by univariate and multivariate analyses. Receiver operating characteristic (ROC) curve analysis was used to identify the significant parameters in multivariate analysis. Cutoff values, sensitivity, specificity, and accuracy with the area under the curve (AUC) > 0.600 were considered significant parameters."

RESULTS

Significant difference were detected in age ($p < 0.001$), temperature ($p < 0.001$), white blood cell count (WBC, $p < 0.001$), C-reactive protein (CRP, $p < 0.001$), neutrophil ($p < 0.001$), neutrophil-to-lymphocyte ratio (NLR, $p = 0.019$), platelet-to-lymphocyte ratio (PLR, $p < 0.001$), platelet count ($p < 0.001$), coefficient of variation of erythrocyte distribution width (RDW-CV, $p < 0.001$), standard deviation of erythrocyte distribution width (RDW-SD, $p < 0.001$), mean platelet volume (MPV, $p < 0.001$), T-bilirubin ($p < 0.001$), and direct bilirubin ($p < 0.001$) between the two groups. CRP, neutrophil, NLR, PLR, platelet count, RDW-CV, RDW-SD, MPV, and direct bilirubin were independent variables for diagnosing complicated appendicitis.

CONCLUSIONS

In patients with acute appendicitis, CRP > 22.95 mg/L, NLR > 5.7, serum D-bilirubin > 6.1 mmol/L, or RDW-SD > 17.7 fl are significantly associated with the presence of complicated appendicitis.

Introduction

Acute appendicitis is a common acute abdominal issue. The morbidity is 1.5–1.9/10 million, and that in males is 1.4-fold higher than in females [1, 2]. Reportedly, the risk of acute appendicitis is 7–8% in a lifetime. About 17–30% of patients present appendiceal perforation, and this proportion is much higher in the elderly [1–3]. Appendicitis can be divided into uncomplicated and complicated appendicitis according to its pathology. Uncomplicated appendicitis has a mild infection and fewer complications and can be

treated with antibiotics. On the other hand, surgery is the primary treatment for complicated appendicitis. Also, early diagnosis and management are crucial to decrease the incidence of complications and the duration of hospitalization.

The diagnosis of acute appendicitis depends on the clinical features, laboratory parameters, and imaging results. Only 60% of patients present typical symptoms, including shifting right lower abdominal pain, fever, nausea, and vomiting [1, 4, 5]. 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 the specificity of the severity [1, 3, 6, 7]. Abdominal ultrasound and computed tomography (CT) scan are used in the diagnosis of appendicitis. According to the literature, the sensitivity and specificity of ultrasound were 86% and 81% due to the influence of the intestinal gas [8, 9]. Although CT has better sensitivity and specificity than ultrasound [1, 10, 11], the high cost and the risk of radiation limits its application. Therefore, evaluation of the type of acute appendicitis based on laboratory tests is essential.

Since the last decade, studies have proved that neutrophil count, neutrophil percentage, neutrophil-to-lymphocyte ratio (NLR), platelet (PLT), mean platelet volume (MPV) and direct bilirubin are valuable parameters in the diagnosis of appendicitis and predicting the complications [1, 12–17]. However, the case numbers were small and the results varied. This study aimed to evaluate the diagnostic value of CRP, WBC, NLR, PLT, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratios (LMR), erythrocyte distribution width (RDW), MPV, and serum bilirubin levels in the type of acute appendicitis. We also established a standard to guide the management of acute appendicitis.

Materials And Methods

Materials

A total of 1514 cases with acute appendicitis at the Beijing Tsinghua Changgung Hospital Gastrointestinal Department (978, 64.6%) and Aerospace Center Hospital General Surgery Department (536, 35.4%) from January 2016 to September 2021 were reviewed in this retrospective study. All cases underwent laparoscopic appendectomy. The inclusion criteria were as follows: 1)age ≥ 14years-old; 2) the pathology proved the diagnosis. The exclusion criteria were as follows: 1) combined with autoimmune diseases; 2) combined with diseases affecting the bilirubin level.

The blood tests were carried out within 12 h before the operation. The complete blood count and blood chemistry (Flow cytometry, Sison Meikang) were performed by the clinical laboratory department. All the cases underwent laparoscopic appendectomy.

The appendix pathology was evaluated by the experienced pathologist from the two hospitals. The four categories of pathology results were simple appendicitis, phlegmonous appendicitis, gangrenous appendicitis, and perforated appendicitis. All the cases were divided into uncomplicated appendicitis

(simple appendicitis and phlegmonous appendicitis) and complicated appendicitis (gangrenous appendicitis and perforated appendicitis) groups.

Data collection

Age, gender, temperature, WCC, CRP, MPV, neutrophil count, neutrophil percentage, lymphocyte count, coefficient of variation of erythrocyte distribution width (RDW-CV), standard deviation of erythrocyte distribution width (RDW-SD), total bilirubin, direct bilirubin, NLR, LMR and PLR were estimated and recorded.

Statistical analysis

All parameters were analyzed by SPSS 25.0 (SPSS, Chicago, IL, USA). Continuous variables of normal distribution were expressed as mean ± standard deviation (mean ± SD) and compared using the t-test. Continuous variables with abnormal distribution were expressed as median and compared using the Kruskal–Wallis H test. The enumeration data were expressed as case numbers and percentages and compared using the chi-square test. Logistic regression analysis was performed as multivariate analysis on parameters with significant differences observed in univariate analysis. The diagnostic accuracy was evaluated by receiver operating characteristic (ROC) curve analysis. The appropriate cutoff values were identified, and sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were calculated for parameters with an area under the curve (AUC) > 0.600. All the tests were two-sided. $p < 0.05$ was considered statistically significant.

Results

The cohort comprised 780 (51.5%) males and 734 (48.5%) females, aged 36±15.135 (range: 14–88)-years-old.

Moreover, 1172 (77.4%) cases constituted the uncomplicated appendicitis group, while the other 342 (22.6%) cases were in the complicated appendicitis group. Age (p0.001), temperature (p<0.001), WCC (p<0.001), CRP (p<0.001), neutrophil percentage (p<0.001), neutrophil (p<0.001), NLR (p<0.001), PLR (p<0.001), PLT (p<0.001), RDW-CV (p<0.001), RDW-SD (p<0.001), MPV (p<0.001), total bilirubin (p<0.001), and direct bilirubin (p<0.001) showed significant difference between groups after univariate analysis (Table 1).

Table 1 Univariate analysis between groups

	Group A	Group B	p
Number of cases	1172	342	
Age (years) †	35 (14–81)	41 (16–88)	0.000
Gender (n)			0.868
Male	606 (51.7%)	174 (50.9%)	
Female	566 (48.3%)	168 (49.1%)	
Temperature (°C) ‡	37.0±0.7	37.5±0.93	0.000
WCC ($\times 10^9$/L) ‡	13.0±3.92	14.24±3.98	0.000
CRP (mg/L) ‡	10.18±50.8	43.29±74.41	0.000
Neutrophil granulocyte (%) ‡	84.4±9.4	86.2±7.73	0.000
Neutrophil ($\times 10^9$/L) ‡	10.79±3.93	12.17±3.67	0.000
NLR ‡	8.21±8.36	9.95±11.88	0.000
LMR ‡	2.43±3.12	1.87±3.43	0.919
PLR ‡	167.53±200.27	191.43±374.31	0.000
PLT ($\times 10^9$/L) ‡	222.5±57.46	225.5±58.21	0.000
RDW-CV (%) ‡	11.9±1.55	12.1±1.36	0.000
RDW-SD (fl) ‡	37.4±12.6	38.5±10.56	0.000
MPV (fl)‡	10.3±14.28	10.1±11.8	0.000
Bilirubin (mmol/l) ‡	14.6±8.78	17.95±10.78	0.000
Direct Bilirubin (mmol/l) ‡	4.24±2.6	5.8±3.8	0.000

†Median (range); ‡Mean (±standard deviation). WCC: white cell count; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratios; LMR: lymphocyte-to-monocyte ratios; PLR: platelet-to-lymphocyte ratios; PLT: platelet count; RDW: red cell volume distribution width; MPV: mean platelet volume.

Logistic regression suggested CRP (p<0.001), neutrophil (p<0.001), NLR (p=0.019), PLR (p<0.001), platelet (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. Factors with AUC>0.600 after ROC curve analysis were CRP (p<0.001), NLR (p<0.001), RDW-SD (p<0.001), and direct bilirubin (p<0.001) (Figure 1, Table 2). The cutoff value of CRP, NLR, RDW-SD, and direct bilirubin is shown in Table 3.

Table 2 Logistic regression and ROC curve in factors associated with complicated appendicitis

	Multivariate analysis			ROC curve Analysis		
	OR	95% CI	p	AUC	95% CI	p
RP (mg/L)	1.008	1.005–1.010	<0.001	0.679	0.642–0.714	<0.001
eutrophil ($\times 10^9$/L)	1.120	1.055–1.189	<0.001	0.589	0.556–0.621	<0.001
LR	0.944	0.900–0.991	0.019	0.603	0.556–0.621	<0.001
LR	1.005	1.003–1.008	<0.001	0.573	0.537–0.607	<0.001
LT ($\times 10^9$/L)	0.996	0.993–1.000	0.039	0.502	0.466–0.535	<0.001
DW-CV (%)	0.809	0.657–0.996	0.045	0.579	0.544–0.610	<0.001
DW-SD (fl)	1.147	1.079–1.219	<0.001	0.605	0.571–0.637	<0.001
PV (fl)	1.067	1.018–1.118	0.007	0.567	0.535–0.601	<0.001
irect bilirubin (mmol/L)	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 ratios; PLR: platelet-to-lymphocyte ratios; PLT: platelet count; RDW: red cell volume distribution width; MPV: mean platelet volume.

Table 3 Proposed cut-off values for significant parameters in prediction of acute complicated appendicitis

	Cutoff value	Sensitivity (%)	Specificity (%)	PPV	NPV	pLLR	nLLR	AUC
CRP (mg/L)	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 (fl)	17.7	82.16	33.45	26.50	86.50	1.23	0.53	0.605
Direct Bilirubin (mmol/L)	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 ratios; RDW: red cell volume distribution width.

Discussion

Acute appendicitis is one of the common acute abdominal issues. The reported morbidity is up to 2% [1, 18]. The diagnosis of appendicitis depends on symptoms, signs, laboratory tests, and imaging results [1, 4, 5]. The primary management for acute appendicitis is surgery, especially for complicated appendicitis [19-22]. Reportedly, the ratio of complicated appendicitis accounts for 18–34% of acute appendicitis [2]. Recent studies suggested that conservative treatment is the first choice for uncomplicated appendicitis. Therefore, easy access and effective standards should be established to distinguish complicated from uncomplicated appendicitis in order to guide the management selection. Parameters, such as temperature, CRP, WBC, NLR, PLR, MPV, RDW-CV, RDW-SD, and bilirubin, might help diagnose complicated appendicitis; however, the efficacy is varied [7, 14-18, 23-25]. The present study analyzed 1514 cases who underwent a laparoscopic appendectomy at two surgery centers. The results suggested that CRP, neutrophil, NLR, PLR, PLT, RDW-CV, RDW-SD, MPV, and direct bilirubin are the independent risk factors associated with complicated appendicitis.

Furthermore, CRP is a serum inflammatory marker and a critical factor associated with complicated appendicitis [2, 14, 17, 26]. It increases rapidly to several-fold of the normal value in the early stage of inflammation (6–12 h) [27]. Interestingly, WBC count is a sensitive indicator during the first 24 h of acute appendicitis, while CRP was sensitive after the first 24 h [27]. Ahmed et al. [28] reported that the probability of appendix perforation increased significantly when CRP>48 mg/dL. A study including 42 acute appendicitis cases found that the sensitivity and specificity of perforated appendicitis were 71% and 100%, respectively, when CRP was >40.1 mg/dL [29]. Choudhary et al. [30] reported that the sensitivity and specificity of perforated appendicitis were 100% and 54%, respectively, when CRP was >6.15 mg/L. Hence, the appropriate cutoff of CRP is crucial for distinguishing complicated appendicitis. After the analysis of 1514 cases, 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 cutoff was lower than that reported in previous studies.

NLR can be obtained from complete blood count. It is a routine and cost-effective blood test during the diagnosis of appendicitis. NLR can effectively elucidate the severity of acute appendicitis [16, 23, 24, 31, 32], but the cutoff is yet controversial. Ishizuka et al. [12] reported that an NLR 8.0 is significantly associated with gangrenous appendicitis based on the analysis of 314 cases that underwent appendectomy. Kahramanca et al. [13] analyzed 897 cases and reported an NLR of 5.74 associated with complicated appendicitis. The sensitivity and specificity of the clinical features were 70.8% and 48.5%, respectively. The current study reported an NLR of 5.7 associated with complicated appendicitis, and the sensitivity and specificity were 82.46% and 32.51%. This finding was similar to that of Shimizu et al. and lower than that of Ishizuka et al. The study[12]proposed that the lower the cutoff value of NLR, the higher the sensitivity of NLR. When the cutoff value was 3.5, it reached the highest sensitivity [33], and the specificity increased when NLR was >5.0 [18]. Further investigation of a large number of cases is needed to find a reasonable cutoff of NLR.

The serum bilirubin level increases due to liver dysfunction during infection, especially sepsis. Hence, bilirubin was included in the evaluation of patients with complicated appendicitis [33-35]. The sensitivity

and specificity of total bilirubin and direct bilirubin in recognizing complicated appendicitis were 48% and 61%, respectively [36]. Sand et al. reported that hyperbilirubinemia had a specificity of 86% for appendiceal perforation or gangrene, while CRP had a specificity of only 35% [37]. Estrada et al. also found that bilirubin levels >1 mg/dL have a three-fold risk of perforated appendicitis [38]. On the contrary, some studies reported no diagnostic value for bilirubin in the prediction of perforated appendicitis [39, 40]. Bilirubin alone is sufficient in identifying patients with acute appendicitis and predicting perforated appendicitis. The significance of bilirubin as a marker is increased when combined with clinical symptoms and other blood markers [39, 41]. In this study, total bilirubin and direct bilirubin levels were significantly elevated in the complicated appendicitis group. Direct bilirubin was found to be the independent risk factor associated with complicated appendicitis with a sensitivity of 47.66% and a specificity of 78.16% when the cutoff was 6.1 mmol/L. Although total bilirubin is available, few studies have reported the efficiency of direct bilirubin. However, this result needs to be substantiated with further studies.

RDW reflects the volume heterogeneity of red blood cells. At present, it is mainly used for the differential diagnosis of anemia. Recent studies reported that the RDW level is altered in some inflammatory and infectious diseases, such as inflammatory bowel disease, celiac disease, acute pancreatitis, rheumatoid arthritis, bacteremia, sepsis, and septic shock [42-45]. Previous studies reported a strong correlation between RDW and inflammatory markers, such as CRP, erythrocyte sedimentation rate, and interleukin 6 [42, 46]. The inflammatory mediators affect the survival of red blood cells in the circulation by suppressing erythrocyte maturation. Thus, newer, larger reticulocytes enter the peripheral circulation and increase the RDW [46]. Narci et al. [47] reported that RDW decreases significantly among patients with acute appendicitis compared to healthy individuals. Conversely, Aktimur et al. [48] and Tanrikulu et al. [49] did not identify any diagnostic value of RDW in acute appendicitis. Jung et al. [50] showed that the RDW level was significantly higher in the complicated appendicitis group compared to the uncomplicated appendicitis group. On the other hand, the parameter did not differ significantly between the appendicitis patients and healthy individuals. Thus, our results indicated that RDW-CV and RDW-SD levels are the independent risk factors associated with complicated appendicitis. RDW-SD had a sensitivity of 82.16% and a specificity of 33.45% for complicated appendicitis when the cutoff was 17.7fl. Therefore, RDW could be used as a parameter to identify complicated appendicitis.

Limitations

Although this was a multicenter study including a large number of cases, it was a retrospective analysis and could not avoid bias. Thus, a randomized controlled trial should be performed for further investigation.

Conclusion

In conclusion, no simple or perfect test is yet available for recognizing complicated appendicitis. According to the current results, CRP > 22.95mg/L, NLR > 5.7, RDW-SD > 17.7fl, and direct bilirubin > 6.1

mmol/L are valuable indicators for the recognition of acute complicated appendicitis, and surgery should be recommended as the primary treatment.

Declarations

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Conflict of interest: None declared.

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Figures

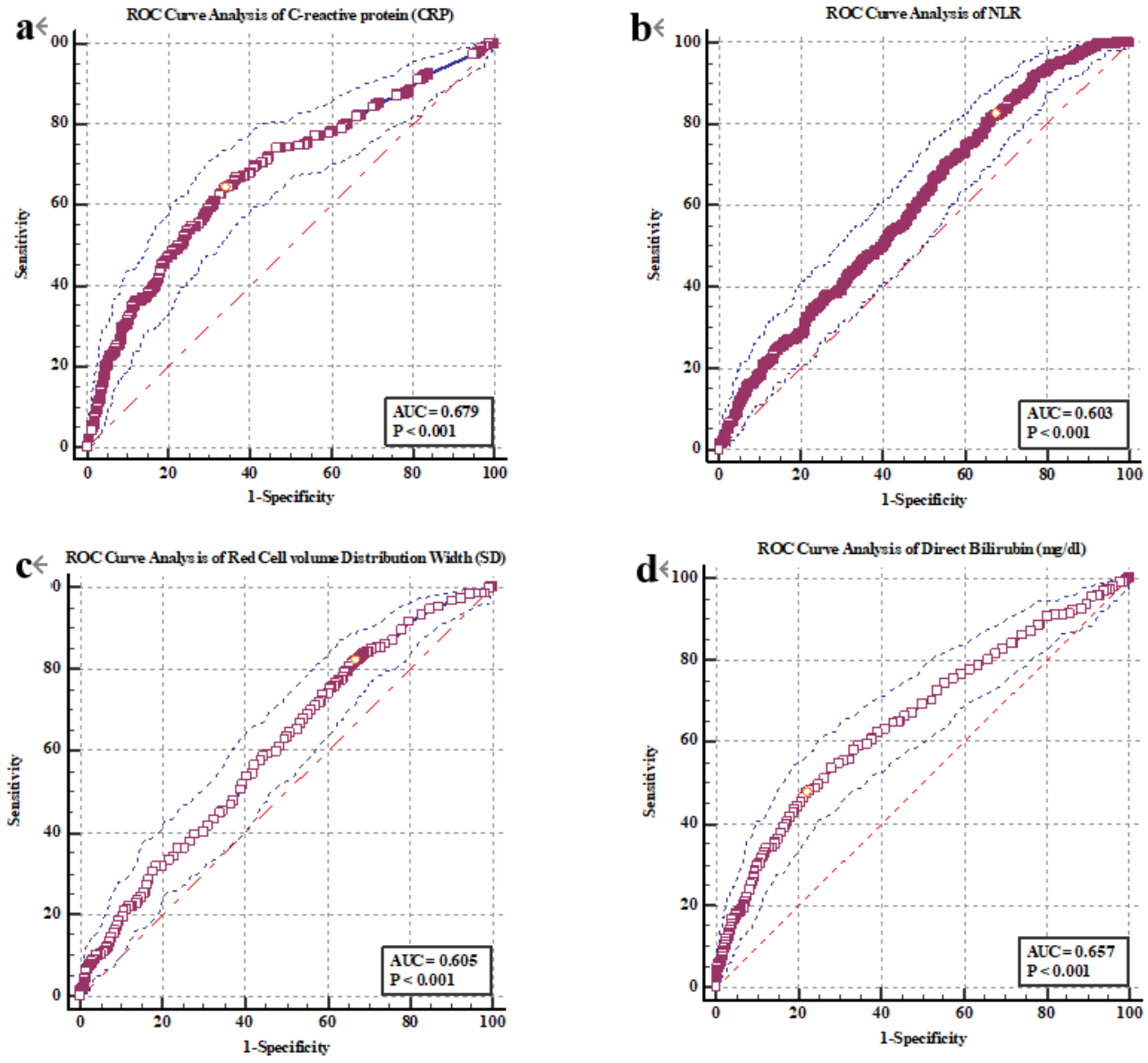

Figure 1. ROC curve analysis of significant parameters in the prediction of acute complicated appendicitis: **(a).** C-reactive protein (CRP), **(b)** neutrophil-to-lymphocyte ratio (NLR), **(c)** Red cell volume distribution width (RDW), **(d)**. serum bilirubin.

Figure 1

See figure for legend.