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Original Article

Diagnostic value of red blood cell distribution width in pediatric acute appendicitis

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Abstract ***Background:*** The aim of this study was to evaluate the diagnostic value of red blood cell distribution width (RDW) in children with acute appendicitis.

Methods: In this retrospective study, a total of 344 children aged ≤18 years with clinically suspected acute appendicitis who underwent appendectomy between January 2007 and January 2014 were reviewed, and 200 healthy controls of the same age group were included. Based on histopathology, the patients were classified as having normal appendix, simple or perforated appendicitis, and preoperative white blood cell count (WBC), C-reactive protein (CRP) and RDW were compared.

Results: Compared with the controls, mean WBC, CRP and RDW were significantly higher in the appendectomy group ($P<0.001$). The children with simple or perforated appendicitis had significantly higher WBC, CRP and RDW than did those with normal appendix ($P<0.001$). Mean WBC and CRP were significantly higher in the children with perforated appendicitis ($P<0.001$), but no statistically significant difference was found in RDW between the simple and perforated appendicitis groups ($P=0.081$).

Conclusions: Children with histologically proven acute appendicitis have higher RDW than children without appendicitis, but the diagnostic value of RDW was not superior to WBC or CRP in children with acute appendicitis. Although higher RDW may be valuable for aiding the diagnosis of acute appendicitis in children, it is not a useful marker for predicting perforated appendicitis.

Key words appendicitis, child, red blood cell distribution width.

Acute appendicitis is one of the most common acute surgical diseases of the abdomen in children.[1] Late presentation or failure to diagnose and correctly manage this condition may lead to perforation, peritonitis, and the complication of infection.[2] Although early diagnosis followed by surgical appendectomy is the current management, approximately 50% of cases of appendicitis in children may have atypical presentation, and non-specific signs and symptoms.[3] Advanced imaging has improved the diagnostic accuracy of acute appendicitis, but it has some disadvantages such as high cost and radiation exposure.[4,5] Several laboratory tests have been used in the evaluation of suspected appendicitis in children, but they had limited ability to differentiate appendicitis from other causes of abdominal pain.[6,7]

Red blood cell distribution width (RDW) is a measure of the variation in size of the circulating erythrocytes, which is routinely reported as part of standard automated complete blood count.[8] During the past few years, extensive research has been done on RDW, and several studies have demonstrated the role of RDW in various forms of inflammatory disease and pathophysiological conditions including septic shock, pulmonary disease, and cardiovascular disease.[9–11] More recently, two studies have examined the diagnostic accuracy of RDW in adult patients with acute appendicitis, and reported slightly different results.[12,13] To our knowledge, however, no study has investigated the role of RDW in acute appendicitis in children, therefore the aim of the present study was to investigate this.

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Methods

After local ethics committee approval, the records of 380 children aged ≤18 years with clinically suspected acute appendicitis who underwent surgical treatment for appendicitis at Mersin University Hospital, Turkey, between January 2007 and January 2014 were reviewed. Children with incomplete medical records, known hematological disease, allergic disease, malignant or inflammatory disease or receiving drugs that can affect hematological parameters were excluded from the study. After exclusion, a total of 344 children who underwent appendectomy and 200 healthy controls of the same age group, who had been admitted to the pediatric clinic and did not have any disease, were included. Demographic data and preoperative complete blood count parameters including white blood cell count (WBC) and RDW, and serum C-reactive protein (CRP) were obtained. All of the patients underwent

Table 1 Subject characteristics

	Appendectomy patients (n = 344) Mean ± SD	Controls (n = 200) Mean ± SD	*P*-value
F/M, n (%)	143 (41.57)/201 (58.43)	96 (48)/104 (52)	0.758
Age (years), (range)	11.38 ± 3.52 (2–18)	11.29 ± 4.25 (2–18)	0.803
WBC (×10/μL)	14.66 ± 4.71	8.44 ± 3.49	<0.001
CRP (mg/L)	42.24 ± 63.09	2.19 ± 3.09	<0.001
RDW (%)	13.51 ± 1.08	12.95 ± 1.91	<0.001

CRP, C-reactive protein; RDW, red blood cell distribution width; WBC, white blood cells.

ultrasonography. Based on postoperative histopathology, the patients were classified as having either normal appendix, simple appendicitis (defined as neutrophilic infiltration of mucosa, submucosa and muscularis propria) or perforated appendicitis (defined as visible perforation at operation or histologically verified perforation). Preoperative WBC, CRP and RDW were compared.

Statistical analysis

All continuous variables are expressed as mean ± SD. Data were compared between the appendectomy group and the controls. WBC, CRP and RDW for the appendectomy group were also compared with regard to histopathology. *t*-Test, analysis of variance and receiver operating characteristic (ROC) curve were used for statistical analysis. Multiple comparisons were made using one-way ANOVA with post-hoc Tukey's test. The ROC curves were used to examine the diagnostic value of WBC, CRP and RDW in children with acute appendicitis. The area under the curve (AUC) was calculated for these parameters. The appropriate cut-offs for WBC, CRP and RDW were determined using maximum sum of sensitivity and specificity. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy were calculated for WBC, CRP and RDW, and statistical significance was set at $P < 0.05$.

Results

The characteristics of the appendectomy group and the controls are listed in Table 1. No statistically significant differences were found between the appendectomy and control groups with regard to gender or age ($P = 0.758$ and $P = 0.803$, respectively). Compared with the controls, mean WBC, CRP and RDW were significantly higher in the appendectomy group ($P < 0.001$, Table 1).

Among the children who underwent appendectomy, 37 (10.75 %) had normal appendix, 182 (52.90 %) had simple appendicitis and 125 (36.33 %) had perforated appendicitis. The children with simple and perforated appendicitis had significantly higher WBC, CRP and RDW than did those with normal appendix ($P < 0.001$, Table 2). WBC, CRP and RDW in the patient with simple and perforated appendicitis are listed in Table 3. Compared with simple appendicitis, mean WBC and CRP were significantly higher in the children with perforated appendicitis ($P < 0.001$). There was no statistically significant difference according to RDW level between the children with simple and perforated appendicitis ($P = 0.081$, Table 3).

The AUC for WBC, CRP and RDW were 0.777, 0.789 and 0.553, respectively (Fig. 1). The appropriate cut-off points determined using maximum sum of sensitivity and specificity for WBC, CRP and RDW were 10 × 10/μL, 5 mg/L and 13.2%, respectively. Sensitivity, specificity, PPV, NPV and overall accuracy for the parameters are listed in Table 4.

Discussion

This is the first study on the role of RDW in children with acute appendicitis. We found that children who underwent appendectomy had significantly higher WBC, CRP, and RDW than the controls. Also, WBC, CRP, and RDW in children with simple and perforated appendicitis were significantly increased compared with those in children with normal appendix. In contrast, there was no difference in RDW between simple and perforated appendicitis.

Accurate diagnosis of acute appendicitis is important, not only to prevent negative appendectomy but also to differentiate simple from perforated appendicitis. To date, several studies have focused on the diagnostic value of laboratory markers in acute appendicitis.[6,7,14,15] In current practice, WBC and CRP are the most widely used laboratory markers for suspected appendicitis in children. WBC has a sensitivity and specificity of 65–85% and 32–82%, respectively, in children with acute appendicitis.[3,7] The sensitivity and specificity of CRP for detecting acute appendicitis in children have been reported as 58–93% and 28–82%, respectively.[3,7]

Table 2 WBC, CRP and RDW in the appendectomy patients

	Normal appendix (n = 37)	Simple and perforated appendicitis (n = 307)	*P*-value
	(mean ± SD)	(mean ± SD)	
WBC (×10/μL)	11.52 ± 4.78	15.04 ± 4.57	<0.001
CRP (mg/L)	10.08 ± 13.83	45.60 ± 65.25	<0.001
RDW (%)	13.01 ± 0.31	13.63 ± 1.08	<0.001

CRP, C-reactive protein; RDW, red blood cell distribution width; WBC, white blood cells.

Table 3 WBC, CRP and RDW in simple vs perforated appendicitis

	Simple appendicitis (n = 182)	Perforated appendicitis (n = 125)	*P*-value
	(mean ± SD)	(mean ± SD)	
WBC (×10/μL)	14.34 ± 3.93	16.06 ± 5.22	<0.001
CRP (mg/L)	30.48 ± 48.03	67.60 ± 79.48	<0.001
RDW (%)	13.52 ± 0.98	13.78 ± 1.20	0.081

CRP, C-reactive protein; RDW, red blood cell distribution width; WBC, white blood cells.

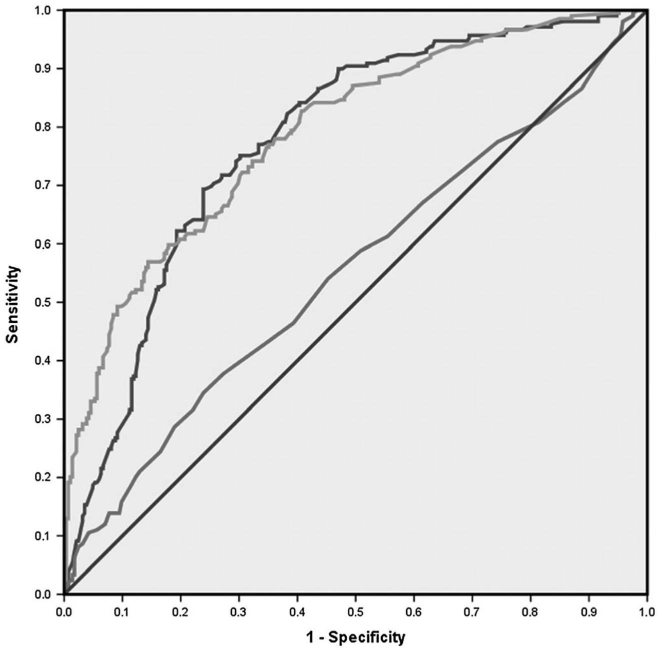

Fig. 1 Receiver operating characteristic curves for (blue) white blood cell count; (green) C-reactive protein; and (red) red blood cell distribution width in predicting acute appendicitis in children.

In this study, specificity and sensitivity of WBC and CRP were consistent with the previous studies, but these markers are not specific indicators of acute appendicitis in children. However, elevated serum WBC and CRP have been identified in chidren with other inflammatory conditions such as pneumonia, gastroenteritis, pharyngitis and urinary tract infections.[3]

Recently, newer laboratory markers have been used for aiding the diagnosis of acute appendicitis.[1,6,7] RDW is simple and automatically measured as part of routine complete blood count. To our knowledge, we are the first to evaluate the value of RDW in children with suspected appendicitis. Two recent studies, however, have examined the role of RDW in appendicitis in adult patients.[12,13] In a retrospective case–control study, Narci *et al.* found a significantly lower RDW in adult patients with acute appendicitis compared with healthy controls.[12] They concluded that the magnitude of difference in RDW seen between acute appendicitis and controls was so slight that RDW had little value in diagnosing acute appendicitis. And in a retrospective multicenter cross sectional study, Tanrikulu *et al*. reported that there was no difference between the acute appendicitis and control groups in terms of RDW.[13] Slightly different results from these studies led us to investigate whether RDW may have value in children with acute appendicitis. Unlike the studies in adults, we showed that mean RDW was significantly higher in children with acute appendicitis.

Table 4 Sensitivity, specificity, PPV and NPV

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
WBC	85.5	56.7	60.8	83.3	69.4
CRP	74.2	66.2	60.7	78.4	69.6
RDW	60.3	49.1	47.2	61.5	53.5

CRP, C-reactive protein; NPV, negative predictive value; PPV, positive predictive value; RDW, red blood cell distribution width; WBC, white blood cells.

Obstruction of the appendiceal lumen due to a variety of causes is a major contributor to the development of appendicitis.[3] Elevation of intraluminal pressure leads to ischemia, bacterial invasion of the wall of the appendix, inflammation, and necrosis. Although the exact mechanism of RDW elevation in children with acute appendicitis is not clearly understood, it may be due to inflammation. There is strong evidence that inflammation can cause inhibition of erythrocyte maturation, leading to elevated RDW.[9,16,17] Lippi *et al.*, however, first reported the existence of a strong, graded and independent association between RDW and inflammation.[16] They concluded that the marked inhibitory effects of the inflammatory cytokines on erythroid progenitor cells could be mainly related to decreased endothelial nitric oxide production, which is known to stimulate the proliferation of erythroid progenitor cells. Elevated RDW has also been reported to be associated with bacteremia. Ku *et al.* found that elevated RDW is a significant predictor of all-cause mortality in patients with bacteremia.[18] They also suggested that clinicians could use increased RDW as a prognostic marker of bacteremia, and should pay additional attention to patients with increased RDW.

Recent studies indicate that oxidative stress and imbalance in the pro-oxidant/oxidant defense system play an important role in the pathogenesis of acute appendicitis.[19,20] Yilmaz *et al.* found that serum nitric oxide and oxidative stress are increased in acute appendicitis.[20] High oxidative stress can also lead to reduced survival of erythrocytes and to increased release of large premature erythrocytes into the peripheral circulation.[9] Generation of reactive oxygen species can also alter erythrocyte membrane glycoproteins and ion channels, which leads to elevated RDW.[21] This may be another mechanism of RDW elevation related to acute appendicitis.

This study was mainly limited by its retrospective nature. We included only children who underwent appendectomy and did not evaluate fluctuation in RDW level. Hence, the present results may need to be confirmed in prospective studies. We examined only WBC, CRP and RDW, but serum levels of oxidative stress markers were not evaluated. Therefore we were unable to identify any association between RDW elevation and oxidative stress in children with acute appendicitis. In another prospective study, a significant number of patients had abdominal pain with unknown etiology.[22] In that study most of the patients had upper respiratory tract infection and/or otitis media or gastroenteritis, constipation and urinary tract infection. In contrast, in the present retrospective study, only children with suspected appendicitis who underwent appendectomy were included, and we were unable to provide the correct diagnosis of the patients with normal appendix.

The present study does have several strengths. This is the first to examine the value of RDW in children with acute appendicitis. High RDW may be affected by several conditions such as hematological disease, allergic disease, malignant and inflammatory disease. In the current study, children with these conditions were excluded. We also compared the parameters with regard to histopathology, that is, normal appendix, and simple and perforated appendicitis. Although RDW was higher in children with acute appendicitis, we were surprised that there was no difference in RDW between simple and perforated appendicitis.

In conclusion, children with histologically proven acute appendicitis have significantly higher RDW than children without appendicitis. RDW does not involve extra cost or specialized equipment, but the diagnostic value of RDW was not superior to WBC or CRP in children with acute appendicitis. Although higher RDW may be valuable for aiding the diagnosis of acute appendicitis in children, it is not a useful marker for predicting perforated appendicitis.

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