

Efficacy of Use of Red Cell Distribution Width as a Diagnostic Marker in Acute Appendicitis

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Abstract

Aim: We aimed to investigate the increase in values of red cell distribution width (RDW) and also the dependence of RDW on leukocyte count (WBC) and C-reactive protein (CRP) values in acute appendicitis (AA).

Materials and Methods: This study includes data collected from 407 patients who were admitted between January 2012 and July 2014 to the emergency service and underwent an operation owing to a diagnosis of AA confirmed by a pathology report. These patients were divided into two groups, namely, non-complicated and complicated appendicitis, according to the results of the operation. The control group consisted of 100 adult patients with similar complaints not having acute abdominal conditions. The age, gender, and WBC, RDW, and CRP levels of the patients on admission were recorded retrospectively.

Results: A total of 350 (86%) of the patient group were diagnosed with non-complicated appendicitis, 34 (8.4%) with plastron appendicitis, and 23 (5.6%) with perforated appendicitis. No significant difference was observed with respect to WBC, RDW, and CRP levels between the AA groups ($p > 0.05$). The WBC, RDW, and CRP values were found to be significantly different in the AA groups from the control group ($p < 0.05$). The sensitivity and specificity of the WBC, RDW, and CRP values in the AA group were 70% and 60%, 41% and 30%, and 51% and 40%, respectively. No dependence of RDW values on WBC or CRP levels was found.

Conclusion: RDW values were found to be significantly higher in the AA group than in the control group. The low sensitivity and specificity values of the RDW test reduce the possibility that it might become a hematologic marker to be used in the definitive diagnosis of AA.

Keywords: Red cell distribution width, acute appendicitis, diagnosis, marker

Introduction

Red cell distribution width (RDW) is a quantitative measurement of difference in the size of circulating erythrocytes, which has a high value if greater heterogeneity in cell dimensions is present (i.e., anisocytosis). RDW is a parameter that is easy and cheap to measure and is routinely checked as part of the full blood count. Normal RDW values range between 11.5% and 14.5% (1). Increased RDW values might be observed in many situations such as a higher production of inactive erythrocytes (hemolysis, which causes the release of premature erythrocytes into the circulation, after blood transfusions, or in cases of deficiencies in iron, vitamin B12, and folic acid). In recent studies, RDW was claimed to be useful for the detection of a

risk of mortality in patients that have cardiovascular disease, acute dyspnea, acute pancreatitis, community-acquired pneumonia, and sepsis (2-5). Acute appendicitis (AA) is the most common cause of acute abdominal pain that requires an emergency surgical operation in adults (6). Individuals have a 7% risk of AA over the course of a lifetime (7). In addition, most patients have characteristic symptoms and findings on physical examination. However, the definitive diagnosis of cases that require emergency operations is not always easy. The important requirement in the case of AA is to perform an emergency operation on an immediate diagnosis. The rate of correct diagnosis of AA is 76%-92% owing to developments and improvements in medicine (8). Rates of perforation and negative appendectomy have not decreased, even though the mortality rate has decreased with recent

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improvements in diagnostic techniques (9). Thus, a diagnosis should be rapidly established using the easiest methods. Otherwise, the development of mortal complications is inevitable in cases where a diagnosis is delayed. A blood test that supports the findings of clinical and physical examinations and imaging of the patient is required for a diagnosis of AA. Currently, there is no marker for the definitive diagnosis of AA prior to performing AA surgery. The need for interventions such as radiological imaging methods and inflammatory tests, as well as invasive procedures such as laparoscopy, has increased owing to the high rates of negative appendectomy and perforation (10). The detection of inflammatory parameters (leukocyte count [WBC], C-reactive protein [CRP] values, etc.) and serial follow-ups are also significant in terms of the diagnosis of AA (11). The aim of our study is to investigate the increase in RDW values, in addition to the dependence of RDW on WBC and CRP values, in AA.

Materials and Methods

In this study, patients diagnosed with AA at Konya Beyhekim Public Hospital emergency service between January 2012 and July 2014 who underwent surgery for AA were investigated following the approval of the Selçuk University School of Medicine ethical committee (number of issue: 2013-336). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review committee on human research. Because the study was a retrospective study, informed consent couldn't be obtained from each patient. Female and male patients older than 18 years who were admitted to the emergency service with a complaint of abdominal pain and/or nausea and vomiting and whose symptoms were compatible with a diagnosis of AA according to their history, findings on physical examination, and laboratory results on admission were examined by abdominal ultrasonography (US) and/or abdominal computed tomography (CT) by radiologists. Patients who were treated medically without surgery were excluded from the study. In total, 407 patients whose diagnoses were confirmed as AA via a pathology report were included in the study. Those diagnosed with AA were divided into two subgroups-non-complicated and complicated (plastron or perforated) appendicitis-according to the results of the operation. The control group consisted of 100 adult patients with similar complaints but with the exclusion of acute abdominal conditions. These patients had diseases such as gastroenteritis, urinary tract infections, renal colic, and non-specific abdominal pain. The age, gender, and WBC, RDW, and CRP levels of the patients on admission were recorded retrospectively.

Biochemical analysis

White blood cell and RDW values were determined from blood samples collected from the patients upon admission (Sysmex XT 2000i). CRP levels were measured using a nephelometric technique (Siemens BN II).

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences 18.0 program (SPSS Inc.; Chicago, USA) Groups were compared using the t-test for continuous variables. The Pearson correlation test was used for the detection of correlation of RDW with other variables. The results were expressed as the mean±standard deviation. The cut-off values of parameters were identified using the

Table 1. Comparison of WBC, CRP, and RDW levels of subjects with complicated and non-complicated acute appendicitis*

	Non-complicated group (n=350)	Complicated group (n=57)	p
WBC (K/ μ L)	11.8±4.5	12.5±4.3	0.99
RDW (%)	13.6±2.1	13.6±2.1	0.94
CRP (mg/L)	27.8±55.8	20.1±45.7	0.11

WBC: white blood cell; RDW: red blood cell distribution width; CRP: C-reactive protein
*Data reported as mean±SD.

Table 2. Comparison of demographic features and WBC, CRP, and RDW levels of subjects in the acute appendicitis and control groups*

	Acute appendicitis group (n=407)	Control group (n=100)	p
Age	31.9±12.7	38.7±11.6	0.001
Male/female	260/147	47/53	0.002
WBC (K/ μ L)	11.9±4.5	9.1±4.6	0.001
RDW (%)	13.6±2.1	13±1.4	0.012
CRP (mg/L)	26.7±54.5	6.9±9.8	0.026

WBC: white blood cell; RDW: red blood cell distribution width; CRP: C-reactive protein
*Data reported as number or mean±SD.

analysis of receiver operating characteristic (ROC) curves for the differentiation of groups. Values of sensitivity and specificity were calculated using different cut-off values. A value of $p \leq 0.05$ was accepted as being statistically significant.

Results

In total, 407 patients with a definitive diagnosis of AA and 100 patients in the control group were investigated. A total of 350 (86%) of the patient group were diagnosed with non-complicated appendicitis, 34 (8.4%) were diagnosed with plastron appendicitis, and 23 (5.6%) were diagnosed as having perforated (complicated) appendicitis. No significant difference was observed with respect to the WBC, RDW, and CRP levels between the complicated and non-complicated AA subgroups ($p > 0.05$) (Table 1). Of the AA group, 260 (63.9%) were male and 147 (36.1%) were female, whereas 47 (47%) of the control group were male and 53 (53%) were female. The mean age of the AA group was 31.9±12.7 years, whereas this was 38.7±11.6 years in the control group. A significant difference was observed between the AA and control groups with respect to age and gender ($p < 0.05$). The mean WBC values were 11.9±4.5 in the AA group and 9.1±4.6 in the control group. RDW values were found to be significantly different between the AA group and the control group ($p < 0.05$) (Table 2). The area under the curve (AUC) was calculated from the ROC curves for the WBC, RDW, and CRP values of the patient groups. The AUC was found to be 0.710 ($p = 0.001$) for WBC, 0.385 ($p = 0.001$) for RDW, and 0.432 ($p = 0.034$) for CRP. Sensitivity was 70% and specificity was 60% according to the ROC curve for WBC, whereas the optimum cut-off was 8.99. Sensitivity was 41% and specificity was 30% according to the ROC curve for RDW, whereas the optimum cut-off was 13.1. Sen-

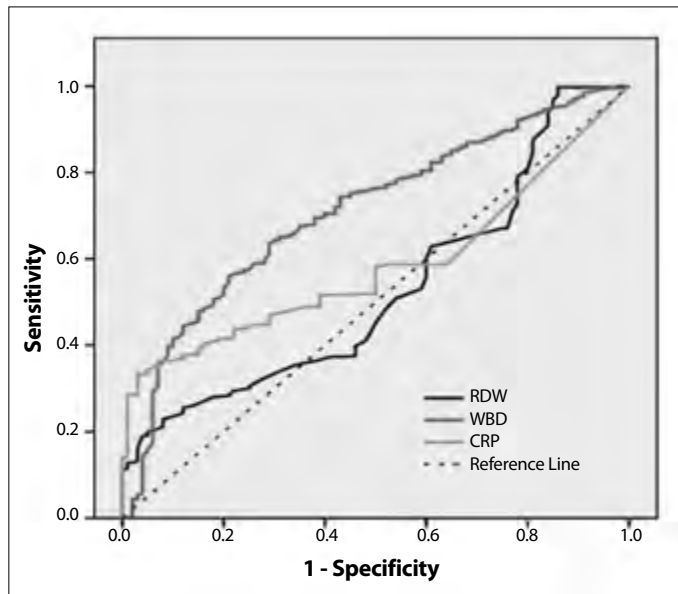


Figure 1. Receiver operating characteristic (ROC) Curves for red blood cell distribution width (RDW), white blood cell (WBC), and C-reactive protein (CRP) in plasma in the diagnosis of acute appendicitis (AA)

sensitivity was 51% and specificity was 40% according to the ROC curve for CRP, whereas the optimum cut-off was 3.3 (Figure 1). A significant correlation was found between WBC and CRP ($p=0.000$) (correlation coefficient=0.221), whereas there was no correlation between RDW and WBC or CRP.

Discussion

This study investigated the relationship between RDW and the severity of disease in AA patients. Significant differences were observed when the median RDW values were compared between the groups. We think that RDW on admission might be useful for prediction of the severity of disease. RDW can be measured by a low-cost laboratory test that is quickly and easily performed using automatic cell counters. RDW, which is a marker that indicates variations in the size of red blood cells (RBCs) in circulation, is usually restricted to the diagnosis of anemia (12). Increases in RDW levels are related to increases in inflammatory markers such as CRP, erythrocyte sedimentation rate, and interleukins (13). We investigated the correlation between RDW, WBC, and CRP, which are inflammatory markers in patients diagnosed with AA. Increased RDW values are related to various medical disturbances and nutritional deficiencies, and are a predictor of early mortality (14). We predicted that RDW might have exceptional value clinically as an independent predictor of the diagnosis of AA, because it is measured by a test commonly performed by clinicians. Recently, inflammation has been stated to be a possible independent predictor of the diagnosis of AA, and RDW might be correlated to inflammatory parameters (15).

Acute appendicitis is the most common cause of acute abdominal surgery, and morbidity and mortality in AA significantly decrease in the event of early diagnosis (6). Mortality has decreased by 85% and operation rates have decreased by 63% with developments in the diagnosis and treatment of AA, whereas discharge rates of patients with abdominal pain have increased by 88% (16). Difficulties in the diagnosis of AA continue despite improvements in diagnostic methods, and rates of

negative appendectomy and perforation are still high (17). Bachmann et al. (18) stated that because the tests used for the diagnosis of AA cannot be used in actual practice, their use can only be suggested. Many parameters (CRP, WBC, neutrophil/lymphocyte ratio, interleukins 4, 5, 6, 10, and 12, tumor necrosis factor-alpha, endotoxin erythrocyte sedimentation rate, procalcitonin, fibrinogen, etc.) have been investigated for the diagnosis of AA in the literature. WBC is used for the diagnosis of AA. Demircan et al. (19) claimed that clinical findings, WBC, other inflammatory markers, abdominal US, and CT should be used as supportive tests for diagnosis. Yang et al. (20) reported that increases in WBC were proportional to the extent of histological inflammation and that CRP values were higher in patients with perforation. Sensitivity was 85% and specificity was 31.9% for WBC in the same study. WBC levels were also significantly higher in the AA group than in the control group in our study. However, no significant difference was observed with respect to WBC, CRP, and RDW levels between the non-complicated and complicated AA subgroups. Sensitivity was found to be 70% and specificity was found to be 60% for WBC.

In all cases of acute inflammation, CRP is a sensitive acute-phase protein of which the level increases according to the duration and severity of inflammation (21). Hallan and Asberg (22) stated that WBC, CRP, and neutrophil levels increase the accuracy of the diagnosis of AA. They also reported a sensitivity of 40%-99% and a specificity of 27%-90%. Asfar et al. (21) claimed that normal CRP levels most probably indicated a non-inflamed normal appendix. They concluded that CRP is more sensitive than WBC and neutrophil count and significantly increases the sensitivity and specificity if used simultaneously. CRP levels were significantly higher in the AA group than in the control group in our study. Sensitivity was 51% and specificity was 40% for CRP.

In numerous recent studies, RDW was found to have extraordinary prognostic value for the prediction of mortality in many clinical conditions (23-25). In addition, RDW is thought to be a marker for many pathological conditions (rheumatoid arthritis, inflammatory bowel disease, colon cancer, celiac disease, etc.) (26-29). Chronic inflammation, aging, malnutrition, and anemia are thought to be underlying factors, but the pathophysiological basis of this relationship is uncertain (30). Similarly, in another study 28-day mortality in patients with sepsis and septic shock has been demonstrated to be related to RDW. (31). This situation supports the relationship between inflammation and RDW. Because AA is an inflammatory process, our study supports the use of RDW as a marker like other inflammatory markers such as CRP and WBC (20-21). Inflammation might be helpful for explaining the relationship between RDW and mortality. It allows the release of abundant new reticulocytes with symptoms of sepsis, and this situation is related to increases in RDW. In addition, high levels of oxidative stress cause increases in RDW by shortening the lifespan of RBCs and promoting the release of abundant immature RBCs into the circulation. In addition, inflammation contributes to morphological changes in RBCs by altering membrane glycoproteins and ion channels in RBCs (32). Şenol et al. (5) emphasized that a high RDW value on admission is an independent marker of mortality in patients with acute pancreatitis and might be used as a prognostic marker. Narci et al. (33) stated that RDW levels in an AA group were low when compared with a control group, and they therefore cannot be used as a suitable marker. They detected a sensitivity of 47% and a specificity of 67% when the optimum cut-off value was 15.6% according to ROC analysis. Similarly, Tanrikulu et al. (34) stated that there was no significant relationship between RDW and AA in their study. However, in our

study RDW values were found to be higher in the AA group than in the control group and therefore RDW is a marker of inflammation and might have predictive value. The sensitivity of RDW was calculated to be 41% and the specificity was calculated to be 30% when the optimum cut-off value was 13.1. As we mention in the Limitations section of our study, the level of RDW may vary with the duration and severity of inflammation. In addition, initial RDW values may be influenced by hospital admission or discharge by the physician. The low sensitivity and specificity of RDW in our study may be caused by this factor. Because the time between the onset of symptoms in our patients, admission to the emergency service, and the onset of treatment is not known, because our study is retrospective, this may have affected sensitivity and specificity (35). There are studies in the literature that show a strong correlation between RDW and inflammatory markers such as CRP and sedimentation rate (15). In our study, no significant correlation was found between RDW, CRP, and WBC.

Study limitations

The most important limitation of this study is that the sample size (patient number) was statistically low. Secondly, because acute changes in RDW might be affected by blood loss or hemolysis, a single measurement of RDW is not sufficient. We could not evaluate changes in RDW levels and did not take variations with time into consideration. Thirdly, samples for RDW measurements were collected in a single center. RDW values in samples collected from different populations for a comparison of clinical outcomes might exhibit differences. Finally, levels of iron, vitamin B12, and folic acid were not measured because the study was retrospective.

Conclusion

It is thought that a rapid, easy, low-cost blood test that supports clinical experience and imaging techniques, gives information about tissue damage in the appendix, and can be performed at the patient's bedside would be optimal. The employment of a specific marker that can lead to early detection even in small centers will enable a safe method of diagnosis in emergency situations, giving a choice of treatment for patients at risk.

Red cell distribution width levels were found to be significantly higher in patients diagnosed with AA in comparison to the control group. The commonly used, low-cost RDW test may be an important hematological parameter for the diagnosis of AA. Its low levels of sensitivity and specificity decrease the possibility of the use of RDW as a marker for the definitive diagnosis of AA. Therefore, further studies are required to investigate the correlation between AA and hematological markers, and, by studying the pathophysiology, to confirm whether or not the correlation is accurate.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University School of Medicine (Decision No: 2013-336).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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