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Ratio of Spleen Diameter to Red Blood Cell Distribution Width

A Novel Indicator for Celiac Disease

Daniel Vasile Balaban, MD, Alina Popp, MD, PhD, Andrei Marian Lungu, MD, Raluca Simona Costache, MD, PhD, Ioana Alina Anca, MD, PhD, and Mariana Jinga, MD, PhD

Abstract: Celiac disease (CD) is currently considerably underdiagnosed, setting the need for developing tools to select patients with probability of CD, who warrant further testing. Red blood cell distribution width (RDW) has been shown in previous studies to be a sensitive predictor for CD, but it lacks specificity. Splenic hypotrophy is also noted frequently in celiac patients.

Our aim was to evaluate if spleen diameter to RDW ratio can be used as an indicator for CD.

We evaluated 15 newly diagnosed CD patients, 52 patients with inflammatory bowel disease, and 35 patients with irritable bowel syndrome (IBS). We evaluated the differences in spleen diameter, RDW, and their ratio among the four groups.

Two-thirds of the CD patients had elevated RDW, compared to 9% in the IBS group. A small spleen was seen in 80% of the celiacs, compared to 21.9% in the ulcerative colitis group, 10% in the Crohn disease group, and 9% in the IBS group. A spleen diameter to RDW ratio under 6 had a sensitivity of 73.3% and specificity of 88.5% in predicting CD, with an AUROC of 0.737.

Spleen diameter to RDW ratio is a simple, widely available score, which can be used to select adult patients with probability of CD.

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Abbreviations: CD = celiac disease, IBD = inflammatory bowel disease, IBS = irritable bowel syndrome, RDW = red blood cell distribution width, CBC = complete blood count, RBC = red blood cell.

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From the ''Dr Carol Davila'' Central Military Emergency University Hospital (BDV, LAM, CRS, JM); ''Carol Davila'' University of Medicine and Pharmacy (BDV, PA, CRS, AIA, JM); ''Alfred Rusescu'' Institute for Mother and Child Care (PA, AIA), Bucharest, Romania; and Tampere Center for Child Health Research (PA), University of Tampere and Tampere University Hospital, Finland.
Correspondence: Daniel Vasile Balaban, "Dr Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania (e-mail: vbalaban@yahoo.com).
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INTRODUCTION

Celiac disease (CD) is an autoimmune systemic disorder triggered by ingestion of gluten in genetically susceptible individuals. It affects 1% of the population[1,2] but only about 20% of patients are currently diagnosed.[3,4] Most of the patients remain undiagnosed because they are either asymptomatic (silent forms) or have vague unspecific symptoms (recurrent abdominal pain, abdominal distension) which are mislabeled as irritable bowel syndrome (IBS), or have extradigestive manifestations (depression, ataxia, neuropathy, infertility, osteoporosis). The latter group, those with nongastrointestinal presentation, is usually treated symptomatically or pathogenically without considering CD as a possible etiology. Given the fact that symptoms of CD or IBS can overlap with those of an inflammatory bowel disease (IBD) activity flare, IBD is also considered in front of a patient presenting with abdominal pain, bloating, or bowel movement changes.

CD serum antibody tests are helpful in case-finding programs for at-risk individuals, but they are quite costly and not easily available. The low diagnostic rate has set a need for developing additional tools which can select patients who warrant confirmatory CD specific tests (serology, upper gastrointestinal endoscopy with duodenal biopsy).

Splenic atrophy and dysfunction and increased red blood cell distribution width (RDW) have been previously reported as being commonly encountered in adult CD patients, but currently available guidelines are not frequently reporting it.[5–7]

Splenic atrophy with associated hyposplenism is a feature of adult CD, with a prevalence varying between 30% to 77%.[8,9] Besides CD, a small spleen with functional hyposplenism can also occur in sickle cell anemia,[10] a low prevalence condition in whites. While splenic hypofunction may improve with a gluten-free diet, in CD patients morphologically the spleen size seems to be irreversible.[11]

RDW is a measure of size variation within the red blood cell (RBC) population, which is reported as part of the standard complete blood count (CBC) by automated hematology analyzers, without any additional costs. RDW is considered a sensitive indicator of nutritional deficiencies affecting RBC production and formation of a heterogeneous RBC population, with variation in cell volume.[12]

Increased RDW even in the presence of normal hemoglobin values has been considered to be a sensitive predictor for CD,[13,14] but it lacks specificity.[15] In CD, RDW can also be used to monitor the dietary efficacy and compliance, as it should normalize in response to the gluten-free diet.[16–18]

In this study, we propose the use of a simple, noninvasive, widely available score—the ratio of spleen diameter to RDW—to detect individuals with probability of CD, who may benefit from further testing. The assumption of using this score is the

TABLE 1. Patient Characteristics

	CD (n = 15)	Crohn Disease (n = 20)	Ulcerative Colitis (n = 32)	IBS (n = 35)
Age (±SD)	36.5 ± 9.9	38.3 ± 14.7	42.7 ± 13.7	37.9 ± 12.2
Gender (%female)	80	55	41	54
Hb (g/dL ± SD)	12.2 ± 1.3	11.8 ± 2.4	13.2 ± 1.5	13.9 ± 1.1
MCV (fL ± SD)	84.2 ± 11.5	82.8 ± 8.3	87.6 ± 5.2	89.3 ± 4.2
RDW (±SD)	14.9 ± 2.2	16.7 ± 3.7	14.3 ± 2.4	13.5 ± 0.7
Spleen size (mm ± SD)	85 ± 13	107 ± 13	104 ± 11	112 ± 12

CD = celiac disease, Hb = hemoglobin, IBS = irritable bowel syndrome, MCV = mean corpuscular volume, RDW = red blood cell distribution width, SD = standard deviation.

fact that both high RDW and splenic atrophy are noted in CD patients and a proportion of a low numerator to a high nominator augments the value of each component used separately.

METHODS

Study Population

We consecutively evaluated 15 newly diagnosed, antibody-positive, biopsy-proven CD adults, 52 IBD patients (20 with Crohn disease and 32 with ulcerative colitis), and 35 IBS patients admitted to our clinic over a period of 24 months, between June 1, 2012, and May 31, 2014. The CD, IBD, and IBS patients were diagnosed based on currently available guidelines.[6,18,19] Patients with coexisting disease associated with splenic atrophy (myeloproliferative disorders, sickle cell anemia, irradiation, autoimmune connective tissue diseases) were excluded from the study.

Ultrasound (US) examinations were performed using the machine GE LOGIQUE 500 by 2 experienced examiners. The longitudinal diameter determined by left intercostal oblique view was used as a measure of spleen size in this study. A small spleen was considered at values under 95 mm in longitudinal axis.[20]

CBC was determined from venous blood samples using a Beckman Coulter Gen S hematology analyzer. The cutoff value of normal RDW was set at 14. We evaluated the differences in spleen diameter, RDW, and their ratio among the four groups.

Statistical Analysis

Data processing and analysis were performed using SPSS Statistics 17.0 (SPSS Inc, Chicago, IL). The significance level was chosen at $\alpha = 0.05$. ANOVA test was used to compare means between the four groups.

Ethics approval was not necessary for this retrospective chart analysis.

RESULTS

Of the 52 patients with IBD, 24 (46%) were women, with a mean age of 41 ± 14.1 years. Among the 35 IBS subjects, 19 (54%) were women, with a mean age of 37.9 ± 12.2 years. There was a significant higher proportion of women (80%) in the CD group in our cohort. The patient characteristics are shown in Table 1.

Crohn disease patients were more likely to be anemic than the other 3 groups, as seen by the mean hemoglobin (Hb) values (the difference, however, did not reach statistical significance). Spleen diameter, RDW, and their ratio values in the study groups are shown in Table 2.

The proportion of CD and Crohn disease patients with elevated RDW (defined as over 14) was significantly higher than those with ulcerative colitis or IBS—67%, 85% versus 37.5% and 9%, respectively. A small spleen (<95 mm) was most frequently seen in CD patients (80%) and less in ulcerative colitis (21.87%), Crohn disease (10%), or IBS (9%).

A spleen diameter to RDW ratio under 6 had a sensitivity of 73.3%, specificity of 88.5%, positive predictive value of 52.4%, and negative predictive value of 95.1% in detecting CD. The AUC (area under the curve) for predicting CD was 0.737 (95% CI: 0.597–0.877) (Figure 1). Only 1 out of 35 (3%) of IBS control subjects had a ratio under 6.

DISCUSSION

In the current study, we evaluate the usefulness of a simple score to detect patients with likelihood of CD. Made up of 2 widely available, inexpensive parameters (RDW is available from routine CBC and spleen size from routine US), this score can be easily calculated in daily clinical practice.

A small spleen (less than 95 mm in longitudinal axis) was noted in a large proportion of CD patients in our study (80%). Previous research has reported similar frequencies in celiac patients, significantly higher than in healthy subjects (78.3%

TABLE 2. RDW, Spleen Diameter, and their ratios in CD Versus Crohn Disease, Ulcerative Colitis, and IBS

	CD (n = 15)	Crohn Disease (n = 20)	Ulcerative Colitis (n = 32)	IBS (n = 35)	*P* Value
Mean RDW (±SD)	14.9 ± 2.2	16.7 ± 3.7	14.3 ± 2.4	13.5 ± 0.7	0.0001
Mean spleen diameter (±SD)	85 ± 13	107 ± 13	104 ± 11	112 ± 12	<0.000001
Mean spleen diameter/RDW (±SD)	5.76 ± 0.73	6.65 ± 1.3	7.37 ± 1.14	8.33 ± 0.87	<0.000001

CD = celiac disease, IBS = irritable bowel syndrome, RDW = red blood cell distribution width, SD = standard deviation.

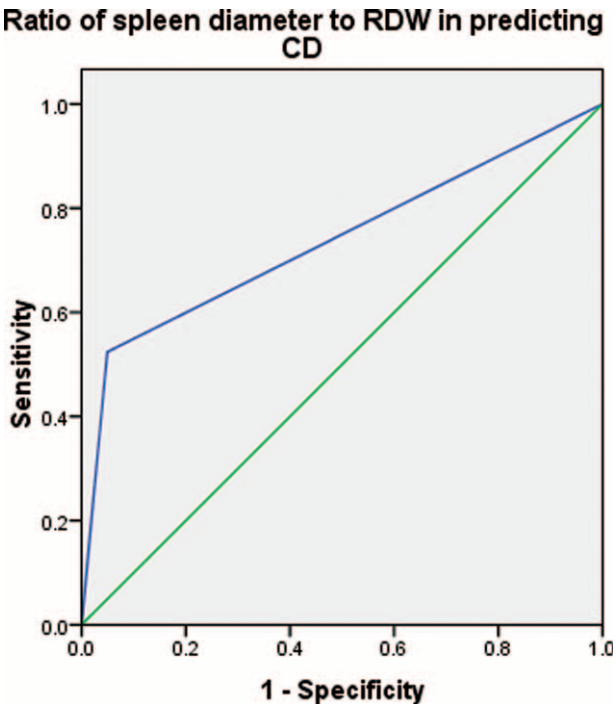

FIGURE 1. Area under the curve (AUC) for a ratio of spleen diameter/RDW under 6 in predicting CD.

and 26.1%, respectively).[21] The paper of Eid et al[8] also demonstrated significant lower splenic volumes in CD patients, compared to healthy population: 162 cm^3 (range 37–321 cm^3) to 215 cm^3 (107–341 cm^3), respectively. The mechanism of splenic atrophy in CD might be related to autoantibody targeting of lymphoid tissue, as shown by Korponay-Szabo et al[22] Considering that splenic length correlates best with body height[23] and that celiac patients are shorter relative to the general population,[24] we also tested the difference in spleen diameter in the 3 groups after adjusting for height and revealed that the difference persisted. There was no statistically significant difference in body weight between the four groups (mean body weight 63.5 kg in CD, 64.5 in Crohn, 67.5 in UC, and 65.7 in IBS).

The second parameter included in this score, RDW, has proven to be a sensitive predictor of CD in previous research. As a marker of anisocytosis due to decreased erythropoiesis, a high RDW is one of the earliest signs of iron deficiency (preceding a drop in Hb or low MCV)—by either increased loss or reduced absorption. Besides its diagnostic value, RDW can also predict intestinal atrophy in selected patients with CD[25] and can be used to monitor the response to GFD.[16] In our cohort, RDW was significantly higher in the CD and Crohn disease groups. Similar rates of high RDW (53.7%, 67%) have been reported in other studies.[13,17]

By combining these 2 sensitive parameters we can easily determine a ratio useful to detect patients, who warrant serologic and histological confirmatory investigations for CD diagnostic. Regarding its sensitivity and specificity, the ratio proved to be better than other daily routine laboratory indices, such as neutrophil-to-lymphocyte ratio (Sn 80%, Sp 41%).[26]

The main limitation of this study is the small sample size. Studies on larger cohort of untreated CD patients would be needed to validate our results and to establish the best cutoff of spleen diameter/RDW ratio.

CONCLUSIONS

Spleen diameter to RDW is a simple, readily available, and reliable score, which can be used to indicate patients with probability of CD. We report for the first time the usefulness of spleen diameter to RDW ratio in selecting patients for CD diagnosis. Further studies with larger samples of CD are needed to validate the diagnostic value of this ratio.

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