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Clinical Relevance of Hematological Parameters and Hemogram-Derived Inflammatory Indices in Newly Diagnosed Pediatric Celiac Disease

Yeni Tanı Almış Pediatrik Çölyak Hastalığında Hematolojik Parametrelerin ve Hemogramdan Türetilen İnflamatuvar İndekslerin Klinik Önemi

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ABSTRACT

Background: Hematological abnormalities are common in celiac disease (CD), but the clinical value of hemogram-derived inflammatory indices in children remains uncertain.

Aim: To evaluate routine hematological parameters and hemogram-derived indices in newly diagnosed pediatric CD and assess their diagnostic and severity-related relevance.

Materials and methods: This retrospective comparative study included 97 children with biopsy-confirmed newly diagnosed CD and 97 age- and sex-comparable controls. Hematological parameters and derived indices were compared between groups. Patients with CD were stratified by tissue transglutaminase immunoglobulin A (tTG-IgA) level (<10× or ≥10× the upper limit of normal) and histopathological severity (Marsh 3A vs 3B–3C). False discovery rate correction, age- and sex-adjusted logistic regression, Spearman correlation, and receiver operating characteristic analyses were performed.

Results: Compared with controls, children with CD had reduced hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hemoglobin-to-red cell distribution width ratio, but increased red cell distribution width; these differences remained significant after correction. Hemogram-based inflammatory indices were not consistently related to diagnosis or disease severity. tTG-IgA levels ≥10× the upper limit of normal were associated with advanced villous atrophy (odds ratio, 3.85; 95% confidence interval, 1.23–12.03; p=0.033). Quantitative tTG-IgA levels did not correlate with hematological markers. The hemoglobin-to-red cell distribution width ratio had the highest but limited discriminatory performance (area under the curve, 0.658).

Conclusion: In newly diagnosed pediatric CD, hematological abnormalities are mainly erythrocyte-related, whereas hemogram-derived inflammatory indices have limited clinical value.

Keywords: Celiac disease, child, blood cell count, biomarkers, immunoglobulin A

ÖZET

Arka Plan: Çölyak hastalığında hematolojik bozukluklar sık görülmekle birlikte hemogramdan türetilen inflamatuvar indekslerin çocuklardaki klinik değeri belirsizdir.

Amaç: Yeni tanı almış pediatrik çölyak hastalarında rutin hematolojik parametreleri ve hemogramdan türetilen indeksleri değerlendirmek ve bunların tanısal ve hastalık şiddetiyle ilişkili önemini araştırmak.

Gereç ve Yöntemler: Bu retrospektif karşılaştırmalı çalışmaya biyopsi ile doğrulanmış yeni tanılı çölyak hastalığı bulunan 97 çocuk ile yaş ve cinsiyet açısından benzer 97 kontrol dahil edildi. Hematolojik parametreler ve türetilmiş indeksler gruplar arasında karşılaştırıldı. Çölyak hastaları doku transglutaminaz immünoglobulin A düzeyine (normal üst sınırın <10 katı veya ≥10 katı) ve histopatolojik şiddete (Marsh 3A veya Marsh 3B–3C) göre sınıflandırıldı. Yanlış keşif oranı düzeltmesi, yaş ve cinsiyete göre düzeltilmiş lojistik regresyon, Spearman korelasyon ve alıcı işletim karakteristiği analizleri uygulandı.

Bulgular: Kontrollerle karşılaştırıldığında çölyak hastalarında hemoglobin, hematokrit, ortalama eritrosit hacmi, hemoglobini ve hemoglobin konsantrasyonu ile hemoglobin/eritrosit dağılım genişliği oranı daha düşük, eritrosit dağılım genişliği ise daha yüksekti; tüm farklar düzeltme sonrasında da anlamlıydı. Hemogramdan türetilen inflamatuvar indeksler tutarlı bir tanısal veya şiddet ilişkisi göstermedi. Doku transglutaminaz immünoglobulin A düzeyinin normal üst sınırın ≥10 katı olması ileri villöz atrofi ile ilişkiliydi (olasılık oranı, 3,85; %95 güven aralığı, 1,23–12,03; p = 0,033). Nicel antikor düzeyleri hematolojik belirteçlerle korelasyon göstermedi. En yüksek ancak sınırlı ayırt edici performans hemoglobin/eritrosit dağılım genişliği oranında saptandı (eğri altında kalan alan, 0,658).

Sonuç: Yeni tanı almış pediatrik çölyak hastalığında hematolojik değişiklikler ağırlıklı olarak eritrositlerle ilişkilidir; hemogramdan türetilen inflamatuvar indekslerin klinik değeri sınırlıdır.

Anahtar Kelimeler: Çölyak hastalığı; çocuk; kan hücresi sayımı; biyobelirteçler; immünoglobulin A

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INTRODUCTION

Celiac disease (CD) develops when dietary gluten induces an immune response in genetically predisposed individuals (1). In children, CD may present with gastrointestinal symptoms, growth failure, anemia, short stature, elevated liver enzymes, or isolated laboratory abnormalities (2).

Pediatric diagnosis relies mainly on total immunoglobulin A and tissue transglutaminase immunoglobulin A (tTG-IgA) testing; a no-biopsy approach may be used when tTG-IgA is ≥10× the upper limit of normal (ULN) and endomysial antibody positivity is confirmed in a second sample (3). Histopathological assessment remains important when tTG-IgA is below the no-biopsy threshold, diagnosis is uncertain, or mucosal injury severity must be evaluated.

Hematological abnormalities are common extraintestinal manifestations of CD, particularly iron deficiency and anemia; folate or vitamin B12 deficiency and other blood count abnormalities may also occur (4, 5). Proximal small intestinal villous injury may impair iron absorption, resulting in lower hemoglobin and erythrocyte indices and higher red cell distribution width.

Routine blood counts also permit calculation of the systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR). Because these measures are obtained from existing hematological data, they have been investigated as accessible indicators of systemic inflammatory activity (6). However, their role in CD remains uncertain. Some adult studies have reported elevated values in newly diagnosed CD (7-9), whereas others found no consistent association with histopathological severity (10). These indices may also change after a gluten-free diet, but their diagnostic and severity-related value remains unclear (11).

Pediatric data on erythrocyte parameters and hemogram-derived inflammatory indices in CD are limited. This study evaluated these markers in newly diagnosed children, examined their associations with tTG-IgA levels and Marsh severity, and explored their ability to distinguish CD from controls.

MATERIALS AND METHODS

Study design

We retrospectively reviewed children diagnosed with celiac disease (CD) at the Department of Pediatric Gastroenterology, Hepatology and Nutrition, Süleyman Demirel University Faculty of Medicine, between January 2018 and December 2025. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (12).

Hematological findings at the time of diagnosis were evaluated in children with CD and compared with those of controls with a similar age and sex distribution. Additional analyses within the CD group were performed according to tTG-IgA category and histopathological severity.

CD group

Eligible patients were aged 0–18 years, had newly diagnosed biopsy-confirmed CD with Marsh 3A–3C histopathology, were consuming gluten, and had complete blood count, tTG-IgA, and total immunoglobulin A results obtained before initiation of a gluten-free diet.

The tTG-IgA threshold of ≥10 x ULN was not used as a diagnostic criterion in this study. Instead, it was used as a predefined serological subgroup threshold because of its clinical relevance in the European Society for Paediatric Gastroenterology, Hepatology and Nutrition diagnostic algorithm (3).

Patients were excluded if they had selective immunoglobulin A deficiency, acute infection or systemic inflammation, chronic inflammatory, autoimmune, hematological, or malignant disease, current immunosuppressive treatment, prior initiation of a gluten-free diet, or incomplete data required for analysis.

Control group

The control group comprised 97 age- and sex-comparable children without clinical findings suggestive of CD. Complete blood counts had been

Table 1. Baseline demographic and hematological characteristics of children with newly diagnosed CD and controls

Variable	CD group (n=97)	Control group (n=97)	p	q
Age, years	9.0 (5.0-12.0)	9.0 (5.0-12.0)	1	-
Sex, male/female	34/63	33/64	1	-
Hemoglobin, g/dL	12.6 (11.2-13.8)	13.5 (12.5-14.0)	<0.001	0.002
Hematocrit, %	37.5 (34.3-40.3)	39.2 (37.2-41.6)	0.003	0.009
MCV, fL	77.5 (70.0-81.5)	80.3 (77.1-83.6)	<0.001	0.002
MCH, pg	26.2 (23.0-27.9)	27.2 (26.2-28.4)	<0.001	0.002
MCHC, g/dL	33.3 (32.3-34.0)	33.9 (33.1-34.7)	<0.001	0.002
RDW, %	14.8 (13.6-16.6)	13.8 (13.4-14.7)	<0.001	0.003
Leukocyte count, $\times10^3$/μL	7.1 (6.3-8.8)	7.1 (6.1-9.5)	0.79	0.808
Neutrophil count, $\times10^3$/μL	3.8 (2.7-4.9)	3.7 (2.7-5.4)	0.31	0.41
Lymphocyte count, $\times10^3$/μL	2.5 (2.1-3.5)	2.3 (1.8-3.0)	0.04	0.103
Monocyte count, $\times10^3$/μL	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.808	0.808
Platelet count, $\times10^3$/μL	313 (269-389)	305 (265-358)	0.533	0.605
MPV, fL	8.1 (7.5-8.8)	7.9 (7.5-8.7)	0.455	0.552
NLR	1.37 (0.84-2.06)	1.75 (0.97-2.87)	0.035	0.084
PLR	118.00 (92.9-157.2)	135.81 (97.1-173.9)	0.090	0.135
MLR	0.20 (0.15-0.27)	0.23 (0.17-0.31)	0.095	0.135
SII	412.15 (288.0-624.0)	493.17 (303.3-964.6)	0.081	0.135
SIRI	0.72 (0.48-1.13)	0.94 (0.44-1.75)	0.094	0.135
HRR (Hb/RDW)	0.87 (0.67-0.99)	0.98 (0.86-1.04)	<0.001	0.002

Data are presented as median (interquartile range) or number. Continuous variables were compared using the Mann-Whitney U test, and sex distribution was compared using Fisher's exact test. q values indicate Benjamini-Hochberg false discovery rate-adjusted p values; the correction was applied to hematological parameters and derived indices. ***HRR****, hemoglobin-to-red cell distribution width ratio;* ***MCH****, mean corpuscular hemoglobin;* ***MCHC****, mean corpuscular hemoglobin concentration;* ***MCV****, mean corpuscular volume;* ***MLR****, monocyte-to-lymphocyte ratio;* ***MPV****, mean platelet volume;* ***NLR****, neutrophil-to-lymphocyte ratio;* ***PLR****, platelet-to-lymphocyte ratio;* ***RDW****, red cell distribution width;* ***SII****, systemic immune-inflammation index;* ***SIRI****, systemic inflammation response index.*

obtained for unrelated clinical reasons, and tTG-IgA results were recorded as unavailable rather than negative because serological testing was not routinely performed. Controls were not eligible if their records indicated an acute infection, a chronic inflammatory, hematological, autoimmune, or malignant condition, or treatment with an immunosuppressive agent.

Data collection and laboratory variables

Electronic hospital records were reviewed to obtain age, sex, and complete blood count results. For children with CD, tTG-IgA values at diagnosis and the Marsh classification reported for duodenal biopsy specimens were also recorded.

The assay-specific ULN for tTG-IgA was 20 U/mL, making 200 U/mL the 10 × ULN threshold. Results reported as >200 U/mL were included in the ≥10 × ULN group but excluded from the primary continuous correlation analysis because exact values were unavailable. In the sensitivity analysis, these values were set at 200 U/mL.

Histopathological classification

Duodenal biopsy findings were obtained from pathology reports and classified as Marsh 3A, 3B, or 3C. For binary subgroup analyses, Marsh 3A was classified as mild villous atrophy, whereas Marsh 3B and 3C were classified as advanced villous atrophy.

Derived hematological indices and study outcomes

All indices were calculated from the same complete blood count. NLR, PLR, and MLR were obtained by dividing the corresponding neutrophil, platelet, and monocyte counts, respectively, by the lymphocyte count. SIRI was calculated as neutrophil × monocyte/lymphocyte, SII as platelet × neutrophil/lymphocyte, and the hemoglobin-to-red cell distribution width

Table 2. Hematological characteristics and histopathological severity according to tTG-IgA level in children with CD

Variable	tTG-IgA ≥10× ULN (n=65)	tTG-IgA <10× ULN (n=32)	p	q
Age, years	9.0 (4.0-12.0)	9.0 (5.0-14.0)	0.55	-
Sex, male/female	21/44	13/19	0.49	-
Hemoglobin, g/dL	12.4 (11.2-13.7)	12.9 (11.9-13.8)	0.16	0.35
Hematocrit, %	37.4 (33.9-40.0)	38.2 (36.1-41.3)	0.34	0.44
MCV, fL	74.9 (69.40-81.50)	79.50 (76.10-81.50)	0.07	0.24
MCH, pg	25 .1 (22.50-27.80)	26.85 (24.93-27.95)	0.04	0.24
MCHC, g/dL	33.1 (32.10-33.70)	33.60 (32.80-34.42)	0.02	0.24
RDW, %	15.0 (13.90-17.20)	13.90 (13.40-15.65)	0.05	0.24
Leukocyte count, $\times10^3$/μL	7.4 (6.5-9.4)	6.9 (5.9-8.2)	0.10	0.26
Neutrophil count, $\times10^3$/μL	3.9 (3.0-4.9)	3.2 (2.4-4.4)	0.18	0.35
Lymphocyte count, $\times10^3$/μL	2.7 (2.1-3.6)	2.3 (1.9-2.7)	0.06	0.24
Monocyte count, $\times10^3$/μL	0.6 (0.4-0.7)	0.5 (0.40-0.62)	0.65	0.74
Platelet count, $\times10^3$/μL	318 (282-404)	295 (257-356)	0.22	0.38
MPV, fL	8.2 (7.6-8.8)	8.0 (7.07-8.5)	0.09	0.26
NLR	1.32 (0.84-2.06)	1.48 (0.93-2.07)	0.65	0.74
PLR	114.7 (88.3-154.7)	128.6 (96.2-164.9)	0.32	0.44
MLR	0.19 (0.14-0.26)	0.21 (0.16-0.27)	0.31	0.44
SII	402.3 (296.0-700.1)	444.0 (270.0-548.5)	0.81	0.81
SIRI	0.72 (0.51-1.12)	0.69 (0.39-1.19)	0.79	0.81
HRR (Hb/RDW)	0.84 (0.65-0.97)	0.93 (0.73-1.02)	0.06	0.21
Advanced villous atrophy (Marsh 3B - 3C), n (%)	59 (90.8)	23 (71.9)	0.03	-

Data are presented as median (interquartile range) or number (%). Continuous variables were compared using the Mann–Whitney U test, and advanced villous atrophy was compared using Fisher's exact test. q values indicate Benjamini–Hochberg false discovery rate-adjusted p values; the correction was applied only to hematological parameters and derived indices. ULN, upper limit of normal; tTG-IgA, tissue transglutaminase immunoglobulin A; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; HRR, hemoglobin-to-red cell distribution width ratio; MPV, mean platelet volume.

ratio (HRR) as hemoglobin/red cell distribution width (RDW). HRR was assessed exploratorily.

The primary analysis compared hematological parameters and derived indices between children with CD and controls. Secondary analyses examined differences according to tTG-IgA category and Marsh severity, correlations with quantitative tTG-IgA, the relationship between tTG-IgA ≥ 10 × ULN and advanced villous atrophy, and diagnostic performance.

Statistical analysis

Statistical analyses were conducted with IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Distributional characteristics were evaluated by histograms, Q-Q plots, and the Shapiro-Wilk test. Continuous data are reported as median (interquartile range), whereas categorical data are given as number (%).

Between-group comparisons of continuous variables were performed with the Mann–Whitney U test. Categorical variables were evaluated using the chi-square test or Fisher's exact test, depending on cell frequencies. The Benjamini–Hochberg procedure was applied to control the false discovery rate (FDR). Unadjusted and adjusted probabilities are reported as p and q, respectively, and $q < 0.05$ was considered statistically significant.

Spearman's rank correlation analysis was used to examine quantitative tTG-IgA values. Separate age- and sex-adjusted logistic regression models were constructed for each marker, and odds ratios were reported per one-standard-deviation increase. Indices with overlapping components were not entered into the same model. The relationship between tTG-IgA ≥ 10 × ULN and advanced villous atrophy was

Table 3. Hematological characteristics of children with CD according to histopathological severity

Variable	Marsh 3B - 3C (n=82)	Marsh 3A (n=15)	p	q
Age, years	9.50 (4.00-12.00)	8.00 (5.50-11.00)	0.642	-
Sex, male/female	29/53	5/10	1.0	-
Hemoglobin, g/dL	12.40 (11.12-13.78)	13.30 (12.55-13.80)	0.115	0.378
Hematocrit, %	37.35 (33.67-40.30)	39.20 (37.05-40.30)	0.178	0.378
MCV, fL	76.7 (69.6-81.2)	80.8 (76.0-83.3)	0.066	0.282
MCH, pg	25.6 (22.6-27.7)	28.0 (25.6-28.5)	0.025	0.213
MCHC, g/dL	33.2 (32.1-33.8)	33.7 (33.0-34.6)	0.057	0.282
RDW, %	15.0 (13.7-16.9)	13.7 (13.1-14.4)	0.014	0.213
Leukocyte count, $\times10^3$/μL	7.1 (6.3-9.0)	7.1 (6.3-8.5)	0.457	0.720
Neutrophil count, $\times10^3$/μL	3.8 (2.8-4.8)	3.1 (2.4-4.8)	0.466	0.720
Lymphocyte count, $\times10^3$/μL	2.5 (2.0–3.5)	2.5 (2.3-2.8)	0.873	0.873
Monocyte count, $\times10^3$/μL	0.5 (0.4-0.7)	0.5 (0.4-0.55)	0.170	0.378
Platelet count, $\times10^3$/μL	310 (270-388)	313 (268-394)	0.826	0.873
MPV, fL	8.1 (7.5-8.8)	8.2 (7.3-8.7)	0.738	0.837
NLR	1.38 (0.9-2.09)	1.19 (0.76-2.06)	0.675	0.837
PLR	121.0 (92.0-158.3)	117.6 (96.2-141.5)	0.738	0.837
MLR	0.21 (0.15-0.28)	0.18 (0.12-0.23)	0.162	0.378
SII	411.5 (299.8-622.0)	493.9 (200.1-649.0)	0.566	0.802
SIRI	0.75 (0.50-1.15)	0.60 (0.32-0.93)	0.202	0.381
HRR (Hb/RDW)	0.84 (0.66-0.97)	0.99 (0.88-1.03)	0.021	0.150

Data are presented as median (interquartile range) or number. Continuous variables were compared using the Mann–Whitney U test, and sex distribution was compared using Fisher's exact test. Marsh 3A was classified as mild villous atrophy, whereas Marsh 3B – 3C was classified as advanced villous atrophy. q values indicate Benjamini–Hochberg false discovery rate-adjusted p values; the correction was applied only to hematological parameters and derived indices. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; HRR, hemoglobin-to-red cell distribution width ratio; MPV, mean platelet volume.

summarized using an odds ratio and 95% confidence interval. Receiver operating characteristic (ROC) performance was evaluated with 1000 bootstrap samples, and Youden index-derived cut-offs were considered exploratory. All tests were two-sided.

Ethical approval and informed consent

Ethical approval was granted by the Süleyman Demirel University Ethics Committee on 9 July 2026 (approval no. 126/18).

RESULTS

Participant characteristics and comparison between the CD and control groups

Overall, 194 children were analyzed, comprising 97 patients with newly diagnosed CD and 97 controls. The CD group comprised 34 boys and 63 girls, and the control group comprised 33 boys and 64 girls. Median age was 9 years in both groups.

Among children with CD, 15 patients (15.5%) had Marsh 3A, 49 (50.5%) had Marsh 3B, and 33 (34.0%) had Marsh 3C histopathology. Tissue transglutaminase immunoglobulin A levels were ≥ 10 × ULN in 65 patients (67.0%).

Compared with controls, children with CD showed lower hemoglobin, hematocrit, erythrocyte indices, and HRR, together with higher RDW. All of these differences retained significance after FDR adjustment. Leukocyte and platelet measures, as well as hemogram-derived inflammatory indices, were comparable between groups; the initially lower NLR was no longer significant after adjustment (Table 1).

Comparison according to tTG-IgA level

Among patients with CD, 32 (33.0%) had tissue transglutaminase immunoglobulin A levels <10× ULN, whereas 65 patients (67.0%) had levels ≥ 10 × ULN. After false discovery rate correction, no hematological

Table 4. Correlations between quantitative tTG-IgA levels and hematological markers in children with CD

Variable	n	Spearman's ρ	p	q
Hemoglobin, g/dL	33	0.07	0.66	0.94
Hematocrit, %	33	0.17	0.32	0.94
MCV, fL	33	0.19	0.28	0.94
MCH, pg	33	0.10	0.54	0.94
MCHC, g/dL	33	0.02	0.87	0.94
RDW, %	33	-0.03	0.83	0.94
Leukocyte count, $\times10^3$/μL	33	0.06	0.70	0.94
Neutrophil count, $\times10^3$/μL	33	0.10	0.57	0.94
Lymphocyte count, $\times10^3$/μL	33	0.10	0.55	0.94
Monocyte count, $\times10^3$/μL	33	-0.01	0.92	0.94
Platelet count, $\times10^3$/μL	33	-0.32	0.06	0.64
MPV, fL	33	0.08	0.62	0.94
NLR	33	0.03	0.86	0.94
PLR	33	-0.31	0.07	0.64
MLR	33	0.01	0.94	0.94
SII	33	-0.14	0.41	0.94
SIRI	33	0.07	0.67	0.94
HRR (Hb/RDW)	33	0.07	0.69	0.94

Spearman's rank correlation analysis was performed in patients with available quantitative tTG-IgA values. Values reported as >200 U/mL were excluded from the primary correlation analysis because exact numerical values were unavailable. q values indicate Benjamini–Hochberg false discovery rate-adjusted p values. tTG-IgA, tissue transglutaminase immunoglobulin A; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; HRR, hemoglobin-to-red cell distribution width ratio.

parameter or derived inflammatory index differed between the tTG-IgA subgroups (Table 2).

Advanced villous atrophy occurred in 59 of 65 patients (90.8%) with tTG-IgA ≥10× ULN and in 23 of 32 patients (71.9%) with lower levels. Accordingly, tTG-IgA ≥10× ULN was associated with higher odds of advanced villous atrophy (odds ratio, 3.85; 95% confidence interval, 1.23–12.03; p = 0.033).

Comparison according to histopathological severity

Compared with the Marsh 3A subgroup, patients with Marsh 3B–3C histopathology showed lower MCH and HRR and higher RDW in the unadjusted analyses. None of these differences retained significance after FDR adjustment. Leukocyte subsets, platelet count, mean platelet volume (MPV), and the derived inflammatory indices were also comparable between the histopathological groups (Table 3).

Correlations between tTG-IgA level and hematological markers

Quantitative tissue transglutaminase immunoglobulin A values were available for 33 patients. No significant correlations were found between tissue transglutaminase immunoglobulin A levels and erythrocyte-related parameters, leukocyte subsets, platelet parameters, HRR, or hemogram-derived inflammatory indices. The results were unchanged in the sensitivity analysis in which values reported as >200 U/mL were truncated at 200 U/mL (Table 4).

Age- and sex-adjusted logistic regression models

After adjustment for age and sex, lower hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were associated with higher odds of CD. Higher RDW and

Table 5. Age- and sex-adjusted single-marker logistic regression models for newly diagnosed CD

Variable	OR (per 1-SD increase)	95% CI	p	q
Hemoglobin, g/dL	0.40	0.26-0.62	<0.001	<0.001
Hematocrit, %	0.47	0.32-0.70	<0.001	0.001
MCV, fL	0.50	0.34-0.72	<0.001	0.001
MCH, pg	0.45	0.30-0.68	<0.001	<0.001
MCHC, g/dL	0.51	0.35-0.74	<0.001	0.001
RDW, %	2.03	1.32-3.10	0.001	0.003
Leukocyte count, $\times10^3$/µL	0.96	0.69-1.34	0.84	0.89
Neutrophil count, $\times10^3$/µL	0.75	0.55-1.03	0.08	0.11
Lymphocyte count, $\times10^3$/µL	1.67	1.09-2.56	0.01	0.03
Monocyte count, $\times10^3$/µL	1.02	0.74-1.39	0.89	0.89
Platelet count, $\times10^3$/µL	1.09	0.80-1.50	0.55	0.63
MPV, fL	1.09	0.80-1.49	0.56	0.63
NLR	0.64	0.45-0.91	0.01	0.03
PLR	0.72	0.52-1.00	0.05	0.08
MLR	0.71	0.50-1.00	0.05	0.08
SII	0.66	0.47-0.92	0.01	0.03
SIRI	0.76	0.53-1.10	0.15	0.20
HRR (Hb/RDW)	0.45	0.31-0.66	<0.001	<0.001

Each hematological marker was evaluated in a separate age- and sex-adjusted logistic regression model. ORs are reported per one-standard-deviation increase in the relevant variable. q values indicate Benjamini–Hochberg false discovery rate-adjusted p values. Derived indices based on overlapping hematological components were not entered simultaneously into the same model to avoid collinearity. OR, odds ratio; CI, confidence interval; SD, standard deviation; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; HRR, hemoglobin-to-red cell distribution width ratio; MPV, mean platelet volume.

lymphocyte count were also associated with increased odds, whereas higher NLR and SII showed inverse associations with CD. Because each marker was analyzed in a separate model and the derived indices contain overlapping blood cell components, these findings require cautious interpretation (Table 5).

Receiver operating characteristic analysis

Receiver operating characteristic analysis showed limited discriminatory performance for all evaluated hematological markers. The highest area under the curve was observed for the hemoglobin-to-red cell distribution width ratio, although its accuracy remained modest (area under the curve, 0.658; 95% confidence interval, 0.580–0.728). Other erythrocyte-related parameters had area under the curve values ranging from 0.623 to 0.651, whereas neutrophil-to-lymphocyte ratio and systemic immune-inflammation index showed weaker discriminatory performance. Exploratory cut-off values derived from the Youden index were not externally validated and were therefore not interpreted as clinical diagnostic thresholds (Table 6).

DISCUSSION

The principal finding of this study was that the most prominent complete blood count abnormalities in newly diagnosed pediatric CD were observed in erythrocyte-related parameters, whereas derived indices expected to reflect systemic inflammation did not demonstrate consistent diagnostic or severity-related performance. Hemoglobin, hematocrit, MCV, MCH, MCHC, and HRR were lower, whereas RDW was higher in the CD group. Although advanced villous atrophy was more frequent among patients with tTG-IgA levels ≥10 × ULN, no significant correlations were observed between serological titers and hematological markers when analyzed as continuous variables.

The observed alterations in erythrocyte indices are consistent with the well-established pattern of iron

Table 6. ROC analysis of selected hematological markers for discriminating CD from controls

Variable	AUC	95% CI	Exploratory cut-off	Sensitivity	Specificity
Hemoglobin, g/dL	0.64	0.565-0.715	≤12.400	0.485	0.763
Hematocrit, %	0.62	0.542-0.703	≤37.300	0.474	0.742
MCV, fL	0.64	0.567-0.717	≤75.000	0.433	0.866
MCH, pg	0.65	0.572-0.727	≤25.500	0.464	0.835
MCHC, g/dL	0.64	0.569-0.717	≤33.800	0.722	0.515
RDW, %	0.63	0.559-0.713	≥15.000	0.464	0.794
NLR	0.58	0.504-0.664	≤1.680	0.701	0.515
SII	0.57	0.496-0.651	≤616.036	0.742	0.423
HRR (Hb/RDW)	0.65	0.580–0.728	≤0.90	0.567	0.701

AUC confidence intervals were calculated using 1000 bootstrap samples. Cut-off values were determined exploratorily in the same sample using the Youden index; no external validation was performed. Therefore, these thresholds should not be interpreted as clinical diagnostic cut-offs. AUC, area under the curve; CI, confidence interval; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; HRR, hemoglobin-to-red cell distribution width ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index.

deficiency and malabsorption in CD. Iron deficiency in CD may arise from multiple mechanisms, including impaired absorption secondary to proximal small intestinal injury, inadequate dietary intake, chronic intestinal blood loss, and inflammation-mediated changes in iron metabolism (4, 5). Reduced iron stores may be present in newly diagnosed children even before the development of overt anemia (13). However, because ferritin, serum iron, transferrin saturation, folate, and vitamin B12 data were not available in our study, the observed erythrocyte alterations cannot be directly attributed to a single deficiency mechanism.

Higher RDW and lower HRR indicate the combined effect of increased erythrocyte size heterogeneity and reduced hemoglobin levels. A pediatric study reported that RDW alone did not reliably discriminate villous atrophy, although a specific RDW threshold may be associated with the presence of atrophy (14). In our study, although RDW was significantly different between the CD and control groups, the difference across Marsh subgroups did not remain significant after FDR correction. Similarly, HRR differed in the diagnostic group comparison but did not retain significance in the serological or histopathological subgroup analyses. Therefore, the HRR finding should be interpreted not as an independent biomarker of CD, but rather as an exploratory marker summarizing erythrocyte-related alterations.

The findings regarding systemic inflammatory indices partly contrast with previous literature. Adult studies have reported elevated NLR and PLR values in patients with CD (7, 8), and SII has also been reported to be associated with newly diagnosed adult CD (9). A more recent adult study showed that SII had high performance in discriminating CD from controls and decreased after a gluten-free diet (11). In contrast, another study found no significant differences in SII, NLR, or PLR across histopathological stages, suggesting that these indices may not adequately reflect the degree of villous injury (10). The pediatric population in our study, the exclusion of acute infection and overt systemic inflammation, the control selection, and the use of FDR correction may explain the divergence from previous positive findings.

In the age- and sex-adjusted single-marker models, NLR and SII showed inverse associations with CD; however, the crude group comparisons were no longer significant after FDR correction, and their ROC performance was weak. This discrepancy suggests that these findings may be sensitive to model specification and that statistical association does not necessarily translate into clinically meaningful discrimination. Moreover, the cell counts included in the numerator and denominator of these indices may be influenced by several biological and clinical conditions, particularly systemic inflammation, infection, injury, and physiological stress (6). The predominantly mucosal and gluten-specific nature of the adaptive immune response in CD may also explain why these changes are not consistently reflected in peripheral blood cell distributions.

A tTG-IgA level ≥ 10 × ULN was associated with an approximately fourfold increase in the likelihood of advanced villous atrophy. Previous pediatric and adult series have shown that high tTG-IgA titers are associated with Marsh 3 histopathology and more severe mucosal injury (15-18). However, the presence of Marsh 3B - 3C atrophy in 71.9% of patients in the <10× ULN group indicates that the relationship between serological titer and histological severity is not absolute. Differences between assay methods, the amount and duration of gluten exposure, individual immune responses, and the patchy distribution of mucosal lesions may contribute to serology-histology discordance.

Although lower MCH, higher RDW, and lower HRR in the Marsh 3B - 3C group may suggest that the hematological effects of advanced mucosal injury are more pronounced, these findings were not statistically significant after FDR correction. The small size of the Marsh 3A group, which included only 15 patients, may have limited the statistical power. In addition, the lack of age-specific hematological reference ranges and iron store parameters limits the interpretation of the relationship between histological severity and hematological abnormalities.

The strengths of this study include the evaluation of biopsy-confirmed pediatric patients who were newly diagnosed and had not yet started a gluten-free diet; the use of a control group with a similar age and sex distribution; the simultaneous assessment of erythrocyte parameters and multiple derived inflammatory indices; the application of FDR correction for multiple comparisons; and the handling of upper-limit censoring in tTG-IgA results through sensitivity analysis.

The limitations of this study should be considered. The retrospective, single-center design limits generalizability. Because controls were not screened with CD serology, asymptomatic seropositive cases could not be completely excluded, and the fact that complete blood count testing was requested for different clinical reasons may have introduced selection bias. The inclusion of only patients with Marsh 3A - 3C biopsy findings limits the generalizability of the results to children with potential CD or those diagnosed using a no-biopsy approach. The lack of data on serum iron, ferritin, transferrin saturation, folate, vitamin B12, C-reactive protein, and detailed nutritional status restricts mechanistic interpretation. The absence of age-specific z-scores or anemia definitions across a wide age range may have resulted in residual confounding. Censoring of a large proportion of tTG-IgA results as >200 U/mL led to information loss in the correlation analysis. The small size of the Marsh 3A group, the derivation of ROC cut-off values from the same sample, and the absence of external validation further support the exploratory nature of the findings.

In conclusion, in newly diagnosed pediatric CD, CBC primarily reflects malabsorption-related alterations in the erythrocyte series. In contrast, NLR, PLR, MLR, SII, and SIRI are not consistent or clinically robust markers of diagnosis, serological burden, or villous atrophy severity. A tTG-IgA level ≥10× ULN is associated with a higher likelihood of advanced villous atrophy, but it does not definitively determine individual histological severity. These findings should be validated in multicenter prospective studies incorporating age-specific hematological criteria, iron status, and nutritional markers.

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