ORIGINAL RESEARCH ARTICLE

The Frequency of Hematologic Disorders in Children with Celiac Disease at Shahid Motahari Hospital in Urmia

Farzaneh Javanmard[1], Saman Rahimi serajgah[2]

Published: 27 September 2025

Abstract

Background Celiac disease is an immune-mediated enteropathy characterized by gluten-induced intestinal mucosal damage that induces immune destruction in genetically susceptible individuals. Among its important and relatively common complications are hematologic disorders. This study statistically evaluated the frequency of hematologic abnormalities in children with celiac disease.

Methods In this descriptive cross-sectional study, all children under 16 years of age hospitalized at Shahid Motahari Hospital in Urmia from 2019 to 2021 with biopsy-proven celiac disease according to the Marsh classification were included. The collected data included age, sex, WBC count, hemoglobin level, platelet count, prothrombin time, partial thromboplastin time, and international normalized ratio. All analyses were performed using SPSS version 27.

Results Among the 67 patients enrolled in the study, 6% had leukocytosis, 11.9% had leukopenia, 10.5% had anemia, 9% had thrombocytosis, and 1.5% had thrombocytopenia. Prothrombin time abnormality was observed in 13.5% of patients, and partial thromboplastin time abnormality in 17.9%. Coagulation disorders were more frequent in girls with celiac disease ($p < 0.05$).

Conclusion The most common hematologic abnormality in children with celiac disease was coagulation disorders. A significant association was found between sex and coagulation abnormalities, with girls showing a higher frequency of these disorders.

Keywords Celiac disease, Children, Hematologic disorders, Urmia

✉ Farzan Javanmard
Javanmard.f@umsu.ac.ir

1. Department of Pathology, Urmia University of Medical Sciences, Urmia, Iran
2. Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Received: 1 May 2025 / Revised: 6 August 2025 / Accepted: 12 September 2025

1 Introduction

Celiac disease—also known as celiac sprue or gluten-sensitive enteropathy—is an immune-mediated enteropathy. Its characteristic feature is intestinal mucosal injury caused by gluten-induced immunologic destruction in genetically susceptible individuals. Clinical manifestations fall into two categories: gastrointestinal symptoms such as malabsorption, chronic diarrhea with or without steatorrhea, bloating, abdominal pain, and lactose intolerance; and extra-intestinal symptoms including depression, fatigue, joint pain, osteoporosis, and osteomalacia. Diagnosis is based on serologic testing and duodenal mucosal biopsy.[1]

Gluten found in wheat (containing gliadin), barley, and rye triggers a cellular immune response that ultimately leads to mucosal destruction, particularly in the proximal small intestine. Luminal enzymes digest gluten into peptides and amino acids, including a 33-amino acid gliadin peptide that is resistant to degradation by gastric, pancreatic, and small intestinal proteases.[1,2] Gliadin is deamidated by tissue transglutaminase and subsequently presented to T lymphocytes. These T cells, located beneath the epithelium, produce cytokines that likely contribute to tissue injury and the histopathological alterations observed in the disease.[3] The clinical presentation of celiac disease varies widely, ranging from asymptomatic cases to severe malnutrition. The disease may manifest with classic features of malabsorption (classic celiac disease) or without them (atypical celiac disease). Diagnosis requires both characteristic mucosal abnormalities on intestinal biopsy and positive serologic markers. In cases with negative histology but strongly suggestive symptoms and positive serology, the biopsy specimen should be reviewed by an expert gastrointestinal pathologist before obtaining additional samples.[4]

The prevalence of celiac disease in predominantly white, European descent populations is approximately 0.5–1%.[5] First-degree relatives of affected patients have a prevalence of about 10%. Celiac disease is strongly associated with HLA DQ2 and HLA DQ8.[6] In Iran, its prevalence in the general population is about 3% in serology-based studies and 2% in biopsy-based studies—slightly higher than the global average.[7] Among Iranian children aged 6–12 years, the reported prevalence is 2% (serology) and 0.6% (biopsy).[8]

Celiac disease is also a common cause of various hematologic disorders, the most frequent being anemia, including iron deficiency, folate deficiency, and vitamin B12 deficiency anemia.[9] In the study by Harper et al., iron deficiency was observed in 33% of men and 19% of women, and folate deficiency in 12% of participants, whereas vitamin B12 deficiency was rare (3%).[10] In the study by Montoro-Huguet et al., anemia was present in 23% of patients, including 12% microcytic, 7% normocytic, and 4% megaloblastic anemia.[11] Celiac disease may also present with abnormal platelet counts, with thrombocytosis being more common than thrombocytopenia.[12] In the study by Rwalah et al., leukopenia was observed in 10% (11 of 111) of children under 14 years with celiac disease.[4] In the study by Duetz et al., approximately 18.5% of adults with celiac disease showed elevated PT.[13]. Fisgin et al., in a study of 22 children with celiac disease, reported anemia in 19 patients (86.3%) and anemia accompanied by leukopenia in two patients (9%). Thrombocytopenia alone was observed in one patient (4.5%). Twelve children had iron deficiency anemia; combined deficiencies of iron, zinc, and vitamin B12 occurred in three patients; copper and vitamin B12 deficiency in two patients; vitamin B12 deficiency in two patients; zinc deficiency in two patients; and one child had a combined deficiency of iron, zinc, and copper. Boys had significantly lower hemoglobin levels than girls. These findings suggest that celiac disease should be considered in the differential diagnosis of children presenting with anemia, leukopenia, thrombocytopenia, or prolonged prothrombin time (PT) and partial thromboplastin time (PTT), especially in regions with high prevalence of celiac disease.[14]

Based on our review, no study in Iran has specifically examined the frequency of hematologic disorders in children with celiac disease. Such disorders include various types of anemia, abnormal platelet counts, abnormal white blood cell (WBC) counts, prolonged PT, prolonged PTT, and elevated international normalized ratio (INR).[15] Accurate epidemiologic data on these abnormalities in Iranian children with celiac disease can help improve the quality of life and management of affected patients, and also support the consideration of celiac disease in children presenting with unexplained hematologic abnormalities. Therefore, this study aimed to evaluate the frequency of hematologic disorders in children with celiac disease.

2 Methods

In this descriptive, analytical, retrospective study, 67 children diagnosed with celiac disease and hospitalized at Shahid Motahari Hospital in Urmia between the years 2019 and 2021 were included. The study was approved by the Research Council of Urmia University of Medical Sciences. A census sampling method was used, including all children whose diagnosis of celiac disease was confirmed by pathology reports based on the Marsh classification of duodenal biopsy specimens.[15] In this classification, the histopathologic criteria for celiac disease include intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy.

The variables examined included age, sex, hematologic parameters (WBC count, hemoglobin level, and platelet count), and coagulation tests (PT and PTT). These data were extracted and analyzed using SPSS version 27. WBC count, hemoglobin level, and platelet count were measured using Sysmex XP300 and KX21 analyzers, while coagulation tests were assessed manually. Reference ranges for these variables were defined according to the 9th edition of the Nelson Textbook of Pediatrics.[16] Normal WBC counts were considered: 6,000 to 15,000/μL for ages 6 months to 6 years; 4,500 to 13,500/μL for ages 7 to 12 years; and 5,000 to 10,000/μL for children older than 12 years. Normal hemoglobin values were 10.5 to 12 g/dL for ages 6 months to 6 years; 11 to 16 g/dL for ages 7 to 12 years; 12 to 16 g/dL in girls older than 12 years; and 14 to 18 g/dL in boys older than 12 years. Normal PT ranges were 12.1 to 14.5 seconds for ages 1 to 5 years; 11.1 to 15.7 seconds for ages 6 to 10 years; and 12.1 to 16.7 seconds for ages 11 to 16 years. Normal PTT ranges were 33.6 to 46.3 seconds for ages 1 to 5 years; 31.8 to 43.7 seconds for ages 6 to 10 years; and 33.9 to 46.1 seconds for ages 11 to 16 years. Platelet counts between 150,000 and 450,000/μL were considered normal across all age groups, and normal INR was defined as 0.9 to 1.1.

Descriptive variables were summarized using frequencies and percentages, and quantitative variables were analyzed using t-tests and chi-square tests. Only patients with biopsy-confirmed celiac disease and complete hematologic evaluations were included. Patients diagnosed through non-biopsy methods or with incomplete hematologic testing were excluded. A significance level of $p < 0.05$ was considered.

3 Results

WBC Abnormalities

A total of 67 children with celiac disease, 44 girls (65.7%) and 23 boys (34.3%, were included in the study. The age at diagnosis ranged from 2 to 14 years. The mean age was 7.26 ± 3.44 years for boys and 6.93 ± 3.04 years for girls. The mean age of the overall study population was 7.04 ± 3.16 years (Table 1).

Among the 23 boys included in the study, 19 (82.6%) had normal WBC counts, three (13.1%) had leukocytosis, and 1 (4.3%) had leukopenia. Among the 44 girls, 36 (81.8%) had normal WBC counts, one (2.3%) had leukocytosis, and seven (16%) had leukopenia. Overall, of the 67 patients, 55 (82.1%) had normal WBC counts, four (6%) had leukocytosis, and eight (11.9%) had leukopenia (Table 1). There was no significant association between sex and WBC abnormalities in children with celiac disease ($p = 0.213$).

Hemoglobin Abnormalities

Among the 23 boys in the study, 20 (87%) had normal hemoglobin levels, and three (13%) had anemia; none had polycythemia. All three anemic boys had microcytic anemia, and no cases of normocytic or megaloblastic anemia were observed. Among the 44 girls, 40 (91%) had normal hemoglobin levels, and four (9%) had anemia; none had polycythemia. All four anemic girls had microcytic anemia, with no cases of normocytic or megaloblastic anemia.

Overall, of the 67 patients, 60 (89.5%) had normal hemoglobin levels, and seven (10.5%) had anemia; no cases of polycythemia were observed. All seven anemic patients had microcytic anemia, and there were no cases of normocytic or megaloblastic anemia (Table 2). There was no significant association between sex and hemoglobin abnormalities in children with celiac disease ($p = 0.517$).

Platelet Count Abnormalities

Among the 23 boys in the study, 20 (87%) had normal platelet counts, and three (13%) had thrombocytosis; no cases of thrombocytopenia were observed. Among the 44 girls, 40 (91%) had normal platelet counts, three (6.8%) had thrombocytosis, and one (2.2%) had thrombocytopenia. Overall, 67 patients were included: 60 (89.5%) had normal platelet counts, six (9%) had thrombocytosis, and one (1.5%) had thrombocytopenia (Table 3).

There was no significant difference in platelet abnormalities between boys and girls with celiac disease, indicating no significant association between sex and platelet disorders in children with celiac disease ($p = 0.480$).

PT Disorders

Among the 23 boys included in the study, 22 (95.6%) had normal PT and one (4.4%) had abnormal PT. Among the 44 girls, 36 (81.8%) had normal PT and eight (18.2%) showed PT abnormalities. Overall, out of the 67 patients in the study, 58 (86.5%) had normal PT and nine (13.5%) had abnormal PT (Table 4). A significant difference was observed between boys and girls with celiac disease regarding PT abnormalities, with abnormal PT being more frequent among girls than boys ($p = 0.029$).

Table 1 WBC abnormalities in children with celiac disease

Variable	Normal	Leukocytosis	Leukopenia	Mean	Standard deviation	P-value
Boys	19 (82.6%)	3 (13.1%)	1 (4.3%)	9026	5155	
Girls	2696	36 (81.8%)	1 (2.3%)	7 (16%)	7690	0.213
Total	55 (82.1%)	4 (6%)	8 (11.9%)	8149	3742	

Table 2 Hemoglobin abnormalities in children with celiac disease

Variable	Normal	Microcytic anemia	Mean	Standard deviation	P-value
Boys	20 (87%)	3 (13%)	12.35	1.96	
Girls	40 (91%)	4 (9%)	12.71	1.25	0.517
Total	60 (89.5%)	7 (10.5%)	12.16	1.52	

Table 3 Platelet count abnormalities in children with celiac disease

Variable	Normal	Thrombocytosis	Thrombocytopenia	Mean	Standard deviation	P-value
Boys	121784	20 (87%)	4 (13%)	0	323782	
Girls	83185	40 (91%)	3 (6.8%)	1 (2.2%)	288681	0.480
Total	98661	60 (89.5%)	7 (9%)	1 (1.5%)	300731	

Table 4 PT abnormalities in children with celiac disease

Variable	Normal	Abnormal	Mean	Standard deviation	P-value
Boys	22 (95.6%)	1 (4.4%)	12.82	0.83	
Girls	36 (81.8%)	8 (18.2%)	13.32	2.81	0.029
Total	58 (86.55)	9 (13.5%)	13.15	2.33	

PTT Disorders

Among the 23 boys included in the study, 19 (82.6%) had normal PTT, and four (17.4%) had abnormal PTT. Among the 44 girls, 36 (81.8%) had normal PTT, and eight (18.2%) showed abnormal PTT. Overall, out of the 67 patients, 55 (82.1%) had normal PTT and 12 (17.9%) had abnormal PTT (Table 5). No significant association was observed between gender and abnormal PTT in children with celiac disease ($p = 0.672$).

INR Disorders

Among the 23 boys included in the study, 21 (91.3%) had normal INR, and two (8.7%) had abnormal INR. Among the 44 girls, 33 (75%) had normal INR and 11 (25%) had abnormal INR. Overall, out of the 67 patients, 54 (80.6%) had normal INR and 13 (19.4%) had abnormal INR (Table 6). A significant association was observed between gender and abnormal INR in children with celiac disease, with abnormal INR being more frequent in girls than in boys ($p = 0.021$).

4 Discussion

Our study demonstrated that hematologic abnormalities in children with celiac disease occur in the following order of frequency: coagulation test disorders, leukopenia, microcytic anemia, thrombocytosis, leukocytosis, and thrombocytopenia. In a study by Catal et al. in Turkey, the most common hematologic manifestations in children with celiac disease were microcytic anemia (24.2%), thrombocytosis, and leukopenia.[17]

Other studies have also reported anemia as the most frequent hematologic manifestation, with a prevalence ranging from 12% to 69%.[18-20] In our study, 10.5% of patients had anemia, most commonly microcytic and iron-deficiency related, consistent with previous reports. In celiac patients, iron deficiency is primarily caused by impaired intestinal absorption, although occult gastrointestinal blood loss may also contribute. Iron deficiency anemia that is resistant to treatment can sometimes be the sole manifestation of celiac disease,

Table 5 PTT abnormalities in children with celiac disease

Variable	Normal	Abnormal	Mean	Standard deviation	P-value
Boys	19 (82.6%)	4 (17.4%)	31	3.54	
Girls	36 (81.8%)	8 (18.2%)	32.6	4.3	0.672
Total	55 (82.1%)	12 (17.9%)	32.1	14.4	

Table 6 INR abnormalities in children with celiac disease

Variable	Normal	Abnormal	Mean	Standard deviation	P-value
Boys	21 (91.3%)	2 (8.7%)	1	0.73	
Girls	33 (75%)	11 (25%)	1.1	0.38	0.021
Total	54 (80.6%)	13 (19.4%)	1.07	0.31	

especially in children.[18] In our study, coagulation disorders (abnormal PT, INR, and PTT) were the most frequent hematologic manifestations. Coagulation abnormalities in celiac patients mainly result from impaired vitamin K absorption.[18,21] In the study by Balaban et al., 14% of newly diagnosed celiac patients had prolonged INR, and the mean INR in newly diagnosed patients was higher compared to those on a gluten-free diet and control groups.[21] In a study by Sharma et al. in India on 111 children with celiac disease, 27% had abnormal INR.[22] Cavallaro et al. reported that 18.5% of celiac patients had abnormal PT, and these patients were more likely to have anemia and iron deficiency.[23] Coagulation abnormalities are more pronounced in symptomatic celiac patients and can occasionally present as mild to severe bleeding as the initial manifestation of the disease.[23] Treatment includes injectable vitamin K or fresh frozen plasma in patients with active bleeding, but the mainstay of management is a gluten-free diet.[18]

In our study, abnormal PT and INR were significantly more frequent in girls than in boys with celiac disease. However, no previous studies have specifically evaluated gender differences in coagulation abnormalities. It should be noted that the limited number of patients in our study and the smaller proportion of boys compared to girls may affect the reliability of this finding. After coagulation abnormalities, leukopenia was the second most common hematologic disorder observed in our study. Leukopenia in celiac patients is rare and may result from autoimmune reactions against neutrophil precursors or from deficiencies in folate, vitamin B12, or copper.[18,24] Catal et al. reported that, following anemia, lymphopenia was the most frequent hematologic abnormality, and vitamin B12 levels were significantly lower in children with lymphopenia compared to those without.[17] In a study by Fisgin et al. on 22 children with celiac disease, leukopenia was observed in two patients and was associated with B12 and copper deficiency.[14]

In our study, 7% of patients had thrombocytosis. Thrombocytosis is more common than thrombocytopenia in celiac patients.[25,26] The exact mechanism of thrombocytosis in celiac disease is unknown. Still, it may be related to the release of inflammatory mediators or, in some cases, to iron deficiency anemia or decreased splenic function (hyposplenism).[24] Thrombocytosis can be observed in up to 60% of celiac patients.[18] In studies by Dupond and colleagues, 14 of 23 celiac patients had thrombocytosis, which was associated with higher disease activity.[27] In our study, 6% of patients had mild leukocytosis, which was less frequent than leukopenia. A review of the literature indicates that leukopenia is reported more frequently than leukocytosis in celiac patients.[16,18,24] Leukocytosis usually occurs in more severe cases of the disease, particularly in patients who have not adhered to a long-term gluten-free diet[28]. The least common hematologic abnormality in our study was thrombocytopenia, observed in only one of 67 patients. Thrombocytopenia is rare in celiac disease and may result from autoimmune mechanisms.[16,18,29] In some cases, it can be associated with idiopathic thrombocytopenic purpura in children with celiac disease.[29,30]

5 Conclusion

In this study, the most common hematologic manifestation in children with celiac disease was coagulation disorders, followed by microcytic anemia. The frequency of coagulation abnormalities was significantly higher in girls than in boys.

The pattern of hematologic manifestations observed in our study differed somewhat from that reported in studies conducted in other countries, which may be attributable to differences in dietary habits, the use of supplemental treatments before diagnosis (such as oral iron preparations), or delayed disease diagnosis in our country. Overall, assessment of hematologic parameters in children with celiac disease is essential, as these manifestations may represent the first sign of the disease, particularly in pediatric patients.

The main limitation of our study was the small sample size. It is recommended that multicenter studies with a larger number of patients and additional variables, including iron and copper levels, be conducted.

Declarations

Acknowledgments
Not applicable.

Artificial Intelligence Disclosure
No artificial intelligence tools were used to generate or analyze data in manuscript preparation.

Authors' Contributions
All authors actively participated in all stages of the study, including execution, analysis, and manuscript writing, and have reviewed and approved the final version of the manuscript.

Availability of Data and Materials
The data and materials used in this study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that they have no conflicts of interest related to the authorship or publication of this article.

Consent for Publication
Not applicable.

Ethical Considerations
This study was approved by the Research Deputy of Urmia University of Medical Sciences under the Code of Ethics IR.UMSU.REC.1401.139.

Funding
No funding was received for the preparation of this manuscript.

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