



Original Article

Clinical spectrum of pediatric celiac disease based on histopathological and endoscopic findings

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Received: 12 September 2025

Accepted: 10 March 2026

Published: 01 May 2026

DOI

10.25259/IJHS_231_2025

Quick Response Code:



ABSTRACT

Objectives: Celiac disease (CD) is a chronic autoimmune enteropathy triggered by gluten ingestion in genetically susceptible individuals. In children, it presents with a wide range of clinical, endoscopic, and histopathological manifestations, often extending beyond classical gastrointestinal symptoms. Understanding these patterns is essential for early diagnosis and effective management. This study aimed to comprehensively describe the clinical presentations, endoscopic features, and histopathological patterns of pediatric CD and to explore the associations between these parameters and additional upper gastrointestinal lesions at King Saud Medical City (KSMC), Riyadh, Saudi Arabia.

Methods: A retrospective analytical observational study was conducted at KSMC, Riyadh, Saudi Arabia. The study included 58 pediatric patients aged 1–14 years diagnosed with CD between January 2015 and April 2024. Data on demographics, clinical presentations, serological markers, endoscopic findings, histopathological classifications, and associated conditions were extracted from medical records. Statistical analyses were performed using the Statistical Package for the Social Sciences version 27, with Chi-square and Fisher's exact tests applied to evaluate associations.

Results: The mean age at diagnosis was 10.8 ± 4.2 years, with a female predominance (63.8%). Abdominal pain (53.4%), anemia (46.6%), diarrhea (22.4%), and weight loss (27.6%) were the most common symptoms. Endoscopic evaluation revealed scalloping in 46.6% of patients, gastritis in 48.3%, and esophagitis in 10.3%. Histopathological assessments showed Marsh III lesions in 94.8% of patients, with complete villous atrophy in 50.0% and crypt hyperplasia in 96.6%. Additional upper gastrointestinal lesions, including duodenal mucosal changes and nodular mucosa, were observed in nearly half of the cohort. However, no statistically significant associations were identified between endoscopic findings and Marsh classifications ($p > 0.05$).

Conclusion: Pediatric CD in this cohort was characterized by heterogeneous clinical symptoms, frequent endoscopic abnormalities, and advanced histopathological changes at diagnosis. The lack of correlation between endoscopic and histopathological findings highlights the continued necessity of duodenal biopsy for accurate diagnosis. Early recognition and multidisciplinary care remain essential to address both gastrointestinal and systemic manifestations of the disease. Clinicians should maintain a high index of suspicion and incorporate routine serological screening and timely biopsy in at-risk children to ensure earlier detection and improved outcomes.

Keywords: Celiac disease, Endoscopy, Gastrointestinal lesions, Histopathology, Pediatrics

How to cite this article: Albogami A, Islam H, Fagih MA, Aodah A, Khormi MA, Alawfi A, *et al.* Clinical spectrum of pediatric celiac disease based on histopathological and endoscopic findings. Int J Health Sci (Qassim). 2026;20:179-88. doi: 10.25259/IJHS_231_2025

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals. In pediatric patients, clinical presentation varies widely, ranging from classic symptoms such as diarrhea, abdominal distension, and growth failure to non-gastrointestinal manifestations including anemia, delayed puberty, and neuropsychiatric issues. The diagnosis relies on a combination of serological markers and confirmatory histopathological evaluation, typically revealing villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes.^[1,2] Histopathological assessment remains a gold standard in evaluating disease severity and therapeutic response, but its interpretation in children requires attention to age-specific mucosal features.^[1,2] Understanding these nuances is essential, as variations in biopsy interpretation may lead to under- or over-diagnosis.^[3]

Epidemiologically, CD affects approximately 1% of the global population, with a rising prevalence noted in both developed and developing regions due to improved screening and greater clinical awareness.^[1,2] In the Middle East, studies estimate prevalence rates ranging between 0.5% and 2%, with particularly increasing detection among children as serologic testing and diagnostic endoscopy become more widely available.^[3,4] In Saudi Arabia, national screening initiatives and improved laboratory diagnostics have contributed to earlier identification of pediatric cases, emphasizing the need for continued research into disease patterns and associated findings.^[5]

Recent multinational data demonstrate substantial regional variation in the incidence of pediatric CD, highlighting the influence of geographic, environmental, and genetic factors on disease expression.^[6] This variability underscores the need for region-specific studies to better contextualize pediatric presentations and diagnostic patterns.^[7]

CD in children manifests through a wide range of gastrointestinal and extraintestinal symptoms that can delay diagnosis and treatment.^[4] While duodenal biopsy remains the diagnostic gold standard, endoscopic findings such as scalloping and mucosal atrophy offer supportive evidence. A comprehensive understanding of these interrelated clinical, endoscopic, and histopathological features enhances diagnostic accuracy and guides optimal management.^[5] Esophageal abnormalities, such as erosions or eosinophilic infiltration, are not uncommon and may represent important comorbid conditions.^[8]

Despite the increasing recognition of CD globally, there remains a paucity of data from Saudi Arabia and neighboring Middle Eastern countries addressing the relationship between endoscopic and histopathological findings in pediatric patients.^[8,9] Furthermore, few regional studies have explored

the prevalence of concurrent upper gastrointestinal lesions, such as gastritis and esophagitis, in children newly diagnosed with CD.^[10] These gaps limit the understanding of disease presentation and may affect diagnostic accuracy in local clinical practice. Addressing these gaps, the present study provides a comprehensive analysis of clinical, endoscopic, and histopathological correlations within a Saudi pediatric population.

CD represents a growing health concern among children worldwide and particularly in Saudi Arabia, where awareness of autoimmune disorders is increasing. Delayed or missed recognition can lead to long-term complications such as growth retardation, nutritional deficiencies, and associated autoimmune diseases. The persistence of advanced mucosal damage at the time of diagnosis in many children indicates substantial histopathological involvement at presentation; however, the diagnostic interval (e.g., time from symptom onset to diagnosis) was not measured in this study, and no inference regarding diagnostic delay can be made.^[11] Given the diagnostic challenges and variable endoscopic appearances, a systematic evaluation of clinical, endoscopic, and histopathological features is essential to improve diagnostic accuracy and patient outcomes. Therefore, this study aimed to comprehensively describe the clinical presentations, endoscopic findings, and histopathological patterns of pediatric CD, while exploring potential associations between these parameters and additional upper gastrointestinal lesions in a Saudi pediatric cohort.

MATERIALS & METHODS

Study design and setting

This was a single-center retrospective cohort study conducted at King Saud Medical City (KSMC), Riyadh, Saudi Arabia, a tertiary care academic hospital that provides specialized pediatric gastroenterology services, including diagnostic endoscopy and histopathological evaluation. The study was designed to investigate the clinical, endoscopic, and histopathological features of pediatric patients diagnosed with CD and to analyze associations among these variables. This design enabled comprehensive data collection and evaluation using existing medical records from a defined period (January 2015 to April 2024).

Study population

The study population consisted of 58 pediatric patients aged between 1 and 14 years who were diagnosed with CD and underwent upper gastrointestinal endoscopy and duodenal biopsy between January 2015 and April 2024 at KSMC. This age group was selected because it represents the most vulnerable developmental period, during which delayed diagnosis of CD can lead to growth failure, nutritional

deficiencies, and long-term complications. In addition, focusing on children up to early adolescence provides a clearer understanding of pediatric-specific clinical, endoscopic, and histopathological features, which may differ from those observed in older adolescents and adults.

During the study period, all eligible pediatric patients who underwent upper gastrointestinal endoscopy with duodenal biopsy for suspected CD at KSMC were identified and included consecutively. Medical records were screened to confirm fulfillment of ESPGHAN diagnostic criteria; patients were excluded only if key variables required for analysis (e.g., endoscopy and biopsy findings and essential clinical/serological data) were missing or if alternative diagnoses were present. Children with suspected CD who underwent endoscopy and biopsy were screened; those fulfilling ESPGHAN criteria and with complete records were included in the final analysis. Patients with missing EMA results were not excluded, as EMA was reported descriptively only and was not included in association testing.

Missing EMA values were primarily attributable to real-world historical workflow factors during the retrospective study window (2015–2024), including variation in ordering practices when tissue transglutaminase immunoglobulin A tissue transglutaminase immunoglobulin A (tTG-IgA) was strongly positive, intermittent differences in test availability/processing pathways, and incomplete transfer of some older paper-based serology records into the electronic system. Because this was a retrospective chart review, unavailable or undocumented EMA results could not be recovered.

Inclusion criteria

The diagnosis of CD was confirmed according to the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) 2020 guidelines.^[11] Patients were considered serologically positive when tTG-IgA levels exceeded 10 times the upper limit of normal (ULN) and/or endomysial antibodies (EMA) were positive on indirect immunofluorescence. Total serum IgA was routinely measured to exclude IgA deficiency before interpreting tTG-IgA results.

Diagnostic pathway and local practice context: Although ESPGHAN 2020 allows a no-biopsy diagnosis in selected children with tTG-IgA $\geq 10 \times$ ULN when additional criteria are fulfilled, our center followed a biopsy-based diagnostic pathway throughout the study period (2015–2024). This reflected local institutional protocol and historical diagnostic practice favoring endoscopic and histopathological confirmation at initial diagnosis, particularly in a tertiary referral setting with heterogeneous presentations and frequent concomitant upper gastrointestinal findings. Accordingly, all included patients underwent upper

gastrointestinal endoscopy with standardized duodenal sampling for confirmatory diagnosis and disease staging.

For histopathological confirmation, duodenal biopsy specimens were evaluated using the Marsh–Oberhuber classification system, which grades villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. A minimum of five biopsy samples (four from the second portion of the duodenum and one from the duodenal bulb) were obtained for each patient to ensure diagnostic reliability and minimize sampling error.

Exclusion criteria

Patients were excluded if their medical records were incomplete, if they had uncertain or alternative diagnoses such as inflammatory bowel disease, or if they had not undergone both endoscopy and biopsy.

Measured variables

The primary variables measured in this study included clinical presentation, such as abdominal pain, diarrhea, weight loss, and anemia. Serological markers were also recorded, including tTG-IgA, anti-endomysial antibodies (anti-EMA), and total IgA levels. Interpretation of serologic markers was guided by established pediatric guidelines, which emphasize the high diagnostic utility of tTG-IgA and the confirmatory value of EMA in children.^[12] Recent pediatric evidence further supports the strong positive predictive value of elevated tTG-IgA titers, particularly at levels $\geq 10 \times$ ULN.^[13,14]

Endoscopic findings were documented, including duodenal scalloping and macroscopic (endoscopic) mucosal atrophy. Histopathological features were assessed separately using the Marsh classification to evaluate microscopic villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. This distinction was maintained throughout the analysis to differentiate endoscopic appearance from histopathological mucosal injury.

Data collection

Data were retrieved retrospectively from both electronic and physical medical records archived at KSMC. A structured data collection sheet was developed to extract relevant variables, including demographic details (age, gender, and date of diagnosis), clinical symptoms, results of serological tests, detailed endoscopic findings, histopathological results, and information on associated autoimmune conditions and nutritional deficiencies. Data abstraction was performed by trained members of the research team under supervision, and all patient identifiers were anonymized to preserve confidentiality. The data were securely stored in password-

protected systems accessible only to the principal investigator and authorized team members. Incomplete records lacking essential clinical, serological, endoscopic, or histopathological information were excluded from the final analysis to ensure data integrity. No statistical imputation was applied, as most variables were categorical. The final sample size ($n = 58$) represented all eligible cases with complete datasets. Patients with missing EMA results were not excluded from the analysis; EMA data were reported descriptively only and were not included in association testing.

To minimize observer bias, endoscopic findings and histopathological evaluations were reviewed independently and blindly by two senior clinicians – a pediatric gastroenterologist and a pathologist – without knowledge of each other's assessments. In cases of discrepancy, results were re-evaluated jointly until consensus was achieved. This dual-review process enhanced the reliability and validity of the recorded findings.

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 27 (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, median, standard deviation, frequencies, and percentages) were used to summarize clinical, endoscopic, and histopathological variables. The Marsh classification was treated as an ordinal variable reflecting progressive mucosal injury; however, because of the small number of cases in certain categories (Marsh I and II) and the overall sample size, non-parametric categorical tests were used instead of ordinal regression or trend analysis. Comparisons between categorical variables (e.g., symptoms vs. Marsh grade, endoscopic findings vs. Marsh grade, and gender vs. histology) were performed using the Chi-square (χ^2) test. When any expected cell count was < 5 , Fisher's exact test was used instead of the Chi-square test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. A priori power analysis was performed using G*Power version 3.1, assuming a medium effect size ($w = 0.3$), $\alpha = 0.05$, power = 0.80, and $df = 4$ for a Chi-square test of association. The calculation indicated that a minimum of 45 participants would provide sufficient statistical power; therefore, the final sample size of 58 was considered adequate. No correction for multiple comparisons was applied; therefore, the analyses should be considered exploratory and interpreted cautiously due to the increased risk of type I error.

Ethical considerations

Ethical approval for this study was obtained from the Institutional Review Board (IRB) of KSMC, Riyadh, Saudi Arabia (IRB Registration No. H-01-R-053). The study was

conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. As the study involved no direct patient contact, all data were anonymized to ensure confidentiality. Patient identifiers were removed or coded, and data were securely stored, with access limited to the principal investigator and authorized team members.

RESULTS

All patients (58/58; 100%) had markedly elevated tTG-IgA levels ($\geq 10 \times$ ULN), consistent with ESPGHAN diagnostic criteria. EMA results were available for 16/58 patients (27.6%) and unavailable for 42/58 patients (72.4%) because of incomplete retrospective laboratory documentation. Among patients with available EMA results, 14/16 (87.5%) were EMA-positive and 2/16 (12.5%) were EMA-negative; both EMA-negative cases also had strongly positive tTG-IgA ($\geq 10 \times$ ULN) and biopsy-confirmed CD. Among EMA-positive cases, 14/14 (100%) had Marsh III lesions. These characteristics are summarized in Table 1.

EMA percentages are reported using the total cohort denominator ($n = 58$); among patients with available EMA results ($n = 16$), 14 (87.5%) were EMA-positive and 2 (12.5%) were EMA-negative.

Endoscopic evaluation revealed that nearly half of the patients (46.6%) presented with duodenal scalloping, whereas none had visible macroscopic (endoscopic) mucosal atrophy. This refers to the absence of gross atrophic changes on endoscopic inspection and should be distinguished from histopathological villous atrophy identified on duodenal biopsy. Esophagitis was identified in 10.3% of cases, and gastritis was observed in 48.3%. Other upper gastrointestinal lesions were common, with duodenal mucosal changes present in 27.6%, nodular mucosa in 10.3%, duodenitis in 8.6%, and other rare lesions in 1.7%, whereas 51.7% of patients had no additional lesions.

Histopathological findings showed that most patients were classified as Marsh IIIc (50.0%), followed by Marsh IIIb (31.0%) and Marsh IIIa (13.8%), with only a small proportion categorized as Marsh II (1.7%) or Marsh I (3.4%). On microscopic histopathological assessment, villous atrophy was complete in half of the patients (50.0%), marked in 31.0%, mild in 13.8%, and normal in only 5.2%. These biopsy-based findings are distinct from the absence of macroscopic endoscopic mucosal atrophy on visual endoscopic examination. Crypt hyperplasia was present in almost all cases (96.6%), and intraepithelial lymphocytosis was universally present (100%).

Regarding associated conditions, 39.7% of patients exhibited nutritional deficiencies, including anemia (31.0%), Vitamin D deficiency (13.8%), combining anemia and Vitamin D deficiency (13.8%), and multiple deficiencies

Table 1: Demographic, clinical, and serological characteristics of pediatric celiac patients ($n=58$).

Variable	Category	n (%)
Gender	Male	21 (36.2)
	Female	37 (63.8)
Age (years)	Mean±SD	10.8±4.2
Nationality	Saudi	45 (77.6)
	Non-Saudi	13 (22.4)
Clinical symptoms	Abdominal pain	31 (53.4)
	Anemia	27 (46.6)
	Weight loss	16 (27.6)
	Diarrhea	13 (22.4)
	Other symptoms*	9 (15.5)
Serology	tTG-IgA positive	58 (100.0)
	EMA positive	14 (24.1)
	EMA negative	2 (3.4)
	EMA missing	42 (72.4)
	Total IgA (median, IQR)	139 (104–181) mg/dL
Endoscopic findings	Scalloping	27 (46.6)
	Gastritis	28 (48.3)
	Esophagitis	6 (10.3)
	Other upper gastrointestinal lesions	28 (48.3)
Histopathology	Marsh IIIc	29 (50.0)
	Marsh IIIb	18 (31.0)
	Marsh IIIa	8 (13.8)
	Marsh II	1 (1.7)
	Marsh I	2 (3.4)

*Other symptoms included constipation, vomiting, bloating, poor appetite, and growth-related complaints (as documented in the medical records). SD: Standard deviation, EMA: Endomysial antibodies, IQR: Interquartile range, tTG-IgA: Tissue transglutaminase immunoglobulin A

(1.7%). Autoimmune comorbidities were also prevalent, with 25.9% diagnosed with diabetes mellitus (DM), 10.3% with hypothyroidism, and 3.4% with both conditions, whereas 60.3% had no autoimmune disease. These findings are summarized in Table 2.

Autoimmune comorbidities and nutritional deficiencies were common in this cohort. Most autoimmune disorders – including type 1 DM (15/58; 25.9%) and hypothyroidism (6/58; 10.3%) – were pre-existing diagnoses, whereas a few were identified concurrently with CD based on laboratory screening. Nutritional deficiencies were also frequent, predominantly anemia (18/58; 31.0%) and Vitamin D deficiency (8/58; 13.8%). Overall, nutritional

and autoimmune comorbidities were frequent, particularly anemia and type 1 DM, underscoring the systemic nature of pediatric CD.

Statistical analyses revealed no significant associations between endoscopic findings (e.g., scalloping and gastritis) and histopathological classifications (Marsh grades I–IIIc) using Chi-square and Fisher's exact tests ($p > 0.05$; Tables 3-6). Similarly, clinical symptoms such as diarrhea, weight loss, and anemia did not significantly differ across Marsh or villous atrophy categories (all $p > 0.05$).

When examining the relationship between endoscopic findings and histopathological severity, no significant associations were observed. Scalloping was present in 46.6% of patients overall, and while it was most common among those with Marsh IIIc (50.0%) and Marsh IIIb (31.0%) classifications, the differences across Marsh stages were not statistically significant, $\chi^2 (4, n = 58) = 3.50, p = 0.478$. Macroscopic endoscopic mucosal atrophy was not observed in any patient, and thus, no statistical test could be performed for this endoscopic variable. This should not be confusing with the high frequency of histopathological villous atrophy identified on biopsy. These results are presented in Table 3.

Scalloping of the duodenal folds was observed in 27 patients (46.6%) but was not significantly associated with higher Marsh grades or villous atrophy severity ($p > 0.05$). Gastritis and esophagitis were identified both endoscopically and histopathologically, confirming the presence of inflammatory changes in the gastric and esophageal mucosa, respectively. Nodular mucosa was consistently used to describe duodenal nodularity, whereas "gastritis" referred to gastric inflammation confirmed by biopsy.

Analysis of gender and clinical symptoms in relation to histopathological severity revealed no statistically significant associations. Male patients were distributed primarily across Marsh IIIb (50.0%) and IIIc (34.5%), whereas females were more frequent in Marsh IIIc (65.5%) and IIIa (75.0%), but these differences were non-significant, $\chi^2 (4, n = 58) = 3.66, P = 0.454$. Similarly, clinical symptoms showed no significant variation by Marsh classification. Diarrhea was reported in 22.4% of patients and was most common in Marsh IIIa (37.5%) and IIIc (24.1%), $\chi^2 (4, n = 58) = 2.31, p = 0.680$. Weight loss was present in 27.6% of patients, more frequently observed in Marsh IIIc (37.9%), but again without statistical significance, $\chi^2 (4, n = 58) = 5.54, p = 0.237$. Abdominal pain, reported by 53.4% of patients, was fairly evenly distributed across Marsh IIIa, IIIb, and IIIc, $\chi^2 (4, n = 58) = 3.67, p = 0.453$. Anemia was present in 46.6% of patients, with the highest frequency in Marsh IIIa (75.0%) and Marsh IIIc (44.8%), yet this association was not significant, $\chi^2 (4, n = 58) = 3.94, p = 0.414$. These results indicate that clinical symptoms and gender were not significantly associated with Marsh classification [Table 4].

Table 2: Endoscopic, histopathological, and associated findings in pediatric celiac patients (n=58).

Domain	Variable	Category	n (%)
Endoscopic findings	Scalloping	Yes	27 (46.6)
		No	31 (53.4)
	Macroscopic endoscopic mucosal atrophy	Yes	0 (0.0)
		No	58 (100.0)
	Esophagitis	Yes	6 (10.3)
		No	52 (89.7)
	Gastritis	Yes	28 (48.3)
		No	30 (51.7)
	Other upper gastrointestinal lesions	None	30 (51.7)
		Duodenal mucosal changes	16 (27.6)
		Nodular mucosa	6 (10.3)
		Duodenitis	5 (8.6)
		Other	1 (1.7)
Histopathology	Marsh classification	Marsh IIIc	29 (50.0)
		Marsh IIIb	18 (31.0)
		Marsh IIIa	8 (13.8)
		Marsh II	1 (1.7)
		Marsh I	2 (3.4)
	Villous atrophy severity	Complete	29 (50.0)
		Marked	18 (31.0)
		Mild	8 (13.8)
		Normal	3 (5.2)
	Crypt hyperplasia	Yes	56 (96.6)
		No	2 (3.4)
	Intraepithelial lymphocytosis	Yes	58 (100.0)
	Associated conditions	Autoimmune diseases	None
DM			15 (25.9)
Hypothyroidism			6 (10.3)
DM+Hypothyroidism			2 (3.4)
Nutritional deficiencies		None	23 (39.7)
		Anemia	18 (31.0)
		Vitamin D deficiency	8 (13.8)
		Anemia+Vitamin D deficiency	8 (13.8)
		Multiple (Vitamin D+B12+Folate)	1 (1.7)

DM: Diabetes mellitus

When analyzing gender and clinical symptoms in relation to villous atrophy, no statistically significant associations were found. Male patients were more frequently classified with marked (50.0%) or complete (34.5%) villous atrophy, whereas females predominated in the mild (75.0%) and complete (65.5%) categories, but this difference was non-significant, $\chi^2 (4, n = 58) = 3.66, p = 0.301$. Clinical symptoms also did

not differ significantly across villous atrophy categories. Diarrhea was present in 22.4% of patients, with slightly higher prevalence in the mild group (37.5%), $\chi^2 (3, n = 58) = 2.31, p = 0.512$. Weight loss, observed in 27.6% of patients, was more common in the complete atrophy group (37.9%), $\chi^2 (3, n = 58) = 5.54, p = 0.137$. Abdominal pain was reported by 53.4% of patients, distributed across mild, marked, and

Table 3: Association between endoscopic findings and Marsh classification (n=58).

Endoscopic finding	Marsh I n (%)	Marsh II n (%)	Marsh IIIa n (%)	Marsh IIIb n (%)	Marsh IIIc n (%)	Total n (%)	Chi-square χ^2 (df)	p-value	Cramer's V
Scalloping	2 (3.4)	1 (1.7)	8 (13.8)	18 (31.0)	29 (50.0)	58 (100.0)	3.50 (4)	0.478	0.246
Macroscopic endoscopic mucosal atrophy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	58 (100.0)	—	—	—

Data are presented as n (%). Associations were tested using Chi-square or Fisher's exact test (when expected cell counts were <5). Effect size is reported as Cramer's V. "—" indicates not applicable; statistics are presented only for the variables with analyzable variation. Percentages are based on the table denominator (available case analysis, where applicable). The significance of p-value is 0.05.

Table 4: Association of gender and clinical symptoms with Marsh classification (n=58).

Variable	Category	Marsh I n (%)	Marsh II n (%)	Marsh IIIa n (%)	Marsh IIIb n (%)	Marsh IIIc n (%)	Total n (%)	Chi-square χ^2 (df)	p-value	Cramer's V
Gender	Male	0 (0.0)	0 (0.0)	2 (25.0)	9 (50.0)	10 (34.5)	21 (36.2)	3.66 (4)	0.454	0.251
	Female	2 (100.0)	1 (100.0)	6 (75.0)	9 (50.0)	19 (65.5)	37 (63.8)	—	—	—
Diarrhea	Yes	0 (0.0)	0 (0.0)	3 (37.5)	3 (16.7)	7 (24.1)	13 (22.4)	2.31 (4)	0.680	0.200
	No	2 (100.0)	1 (100.0)	5 (62.5)	15 (83.3)	22 (75.9)	45 (77.6)	—	—	—
Weight loss	Yes	0 (0.0)	0 (0.0)	3 (37.5)	2 (11.1)	11 (37.9)	16 (27.6)	5.54 (4)	0.237	0.309
	No	2 (100.0)	1 (100.0)	5 (62.5)	16 (88.9)	18 (62.1)	42 (72.4)	—	—	—
Abdominal pain	Yes	0 (0.0)	1 (100.0)	4 (50.0)	11 (61.1)	15 (51.7)	31 (53.4)	3.67 (4)	0.453	0.252
	No	2 (100.0)	0 (0.0)	4 (50.0)	7 (38.9)	14 (48.3)	27 (46.6)	—	—	—
Anemia	Yes	1 (50.0)	0 (0.0)	6 (75.0)	7 (38.9)	13 (44.8)	27 (46.6)	3.94 (4)	0.414	0.260
	No	1 (50.0)	1 (100.0)	2 (25.0)	11 (61.1)	16 (55.2)	31 (53.4)	—	—	—

Data are presented as n (%). Associations were tested using Chi-square or Fisher's exact test (when expected cell counts were <5). Effect size is reported as Cramer's V. "—" indicates not applicable; statistics are presented only for the variables with analyzable variation. Percentages are based on the table denominator (available case analysis, where applicable). The significance of p-value is 0.05. df: Degree of freedom.

Table 5: Association of gender and clinical symptoms with villous atrophy (n=58).

Variable	Category	Normal n (%)	Mild n (%)	Marked n (%)	Complete n (%)	Total n (%)	Chi-square χ^2 (df)	p-value	Cramer's V
Gender	Male	0 (0.0)	2 (25.0)	9 (50.0)	10 (34.5)	21 (36.2)	3.66 (4)	0.301	0.251
	Female	3 (100.0)	6 (75.0)	9 (50.0)	19 (65.5)	37 (63.8)	—	—	—
Diarrhea	Yes	0 (0.0)	3 (37.5)	3 (16.7)	7 (24.1)	13 (22.4)	2.31 (4)	0.512	0.200
	No	3 (100.0)	5 (62.5)	15 (83.3)	22 (75.9)	45 (77.6)	—	—	—
Weight loss	Yes	0 (0.0)	3 (37.5)	2 (11.1)	11 (37.9)	16 (27.6)	5.54 (4)	0.137	0.309
	No	3 (100.0)	5 (62.5)	16 (88.9)	18 (62.1)	42 (72.4)	—	—	—
Abdominal pain	Yes	1 (33.3)	4 (50.0)	11 (61.1)	15 (51.7)	31 (53.4)	0.99 (4)	0.805	0.131
	No	2 (66.7)	4 (50.0)	7 (38.9)	14 (48.3)	27 (46.6)	—	—	—
Anemia	Yes	1 (33.3)	6 (75.0)	7 (38.9)	13 (44.8)	27 (46.6)	3.27 (4)	0.352	0.237
	No	2 (66.7)	2 (25.0)	11 (61.1)	16 (55.2)	31 (53.4)	—	—	—

Data are presented as n (%). Associations were tested using Chi-square or Fisher's exact test (when expected cell counts were <5). Effect size is reported as Cramer's V. "—" indicates not applicable; statistics are presented only for the variables with analyzable variation. Percentages are based on the table denominator (available case analysis, where applicable). The significance of p-value is 0.05.

Table 6: Association between endoscopic findings and Marsh classification (n=58).

Endoscopic finding	Category	Marsh I n (%)	Marsh II n (%)	Marsh IIIa n (%)	Marsh IIIb n (%)	Marsh IIIc n (%)	Total n (%)	Chi-square χ^2 (df)	p-value	Cramer's V
Esophagitis	No	2 (100.0)	1 (100.0)	8 (100.0)	16 (88.9)	25 (86.2)	52 (89.7)	1.65 (4)	0.799	0.169
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	4 (13.8)	6 (10.3)	—	—	—
Gastritis	No	1 (50.0)	1 (100.0)	2 (25.0)	10 (55.6)	15 (53.6)	29 (50.9)	3.35 (4)	0.501	0.240
	Yes	1 (50.0)	0 (0.0)	6 (75.0)	8 (44.4)	13 (46.4)	28 (49.1)	—	—	—
Other upper gastrointestinal lesions	None	2 (100.0)	1 (100.0)	5 (62.5)	9 (50.0)	13 (44.8)	30 (51.7)	9.56 (16)	0.889	0.203
	Duodenal mucosal changes	0 (0.0)	0 (0.0)	0 (0.0)	6 (33.3)	10 (34.5)	16 (27.6)	—	—	—
	Nodular duodenal mucosa	0 (0.0)	0 (0.0)	2 (25.0)	1 (5.6)	3 (10.3)	6 (10.3)	—	—	—
	Inflammatory/pathological duodenitis	0 (0.0)	0 (0.0)	1 (12.5)	2 (11.1)	2 (6.9)	5 (8.6)	—	—	—
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.7)	—	—	—

Data are presented as n (%). Associations between endoscopic findings and Marsh classification were assessed using the Chi-square test; Fisher's exact test was used when expected cell counts were <5. Effect size is reported as Cramer's V. "—" indicates that the statistical test and effect-size calculation apply to the overall association only. Marsh classification refers to the standardized grading of mucosal injury in celiac disease (Marsh I–IIIc). Percentages are calculated from the total sample (n=58). Effect size is reported as Cramer's V. "—" indicates that χ^2 /Fisher's exact test and Cramer's V apply to the overall association only, not to individual category rows. The significance of p-value is 0.05.

complete groups, χ^2 (3, n = 58) = 0.99, p = 0.805. Anemia, present in 46.6% of patients, occurred most frequently in the mild group (75.0%) but was not significantly associated with the degree of villous atrophy, χ^2 (3, n = 58) = 3.27, p = 0.352. These findings indicate that neither gender nor clinical symptoms were significantly related to villous atrophy severity [Table 5].

The association between additional endoscopic findings and Marsh classification was examined, and no statistically significant relationships were observed. Esophagitis was identified in 10.3% of patients, most frequently in those with Marsh IIIc (13.8%) and IIIb (11.1%), but this distribution was not significant, χ^2 (4, n = 58) = 1.65, p = 0.799. Gastritis was present in 49.1% of patients, with higher proportions in Marsh IIIa (75.0%) and Marsh IIIc (46.4%); however, this variation was not significant, χ^2 (4, n = 58) = 3.35, p = 0.501. Other upper gastrointestinal lesions were detected in 48.3% of patients, including duodenal mucosal changes (27.6%), nodular duodenal mucosa (10.3%), inflammatory or pathological duodenitis (8.6%), and rare lesions (1.7%). These abnormalities occurred across all Marsh categories, most commonly in Marsh IIIc, but the differences were not statistically significant, χ^2 (16, n = 58) = 9.56, p = 0.889. Overall, endoscopic findings did not demonstrate

a significant association with histopathological severity [Table 6].

DISCUSSION

This study comprehensively evaluated the clinical, serological, endoscopic, and histopathological features of pediatric CD in a Saudi tertiary center. Abdominal pain (53.4%), anemia (46.6%), diarrhea (22.4%), and weight loss (27.6%) were the most common presenting symptoms, consistent with the evolving pediatric phenotype in which classical malabsorptive features are now less dominant. Serological assessments showed universal strong tTG-IgA positivity ($\geq 10 \times$ ULN). EMA documentation was incomplete in this retrospective cohort; among the available EMA results, most were positive.

The absence of macroscopic mucosal atrophy on endoscopy does not contradict the biopsy findings, because endoscopy reflects gross appearance, whereas histopathology assesses microscopic villous injury.

Comparison with existing literature

The predominance of severe mucosal injury aligns with reports from Stefanolo *et al.*,^[8] and Enache *et al.*,^[9] who

similarly documented high rates of Marsh III lesions at diagnosis in pediatric cohorts. Studies by Lupu *et al.*,^[4] and Sahin Y^[10] also reported frequent endocrine and nutritional comorbidities, comparable to the DM and hypothyroidism rates observed in our cohort.

In our cohort, Marsh III lesions were present in 94.8% of patients, including 50.0% with Marsh IIIc. Although this proportion is higher than the 82% reported in a symptomatic pediatric cohort from Uzbekistan, it remains broadly consistent with referral-based pediatric series showing a predominance of Marsh III lesions at diagnosis. For example, Sahin Y^[10] reported Marsh III changes in all biopsy-confirmed pediatric cases (100%), with Marsh IIIa, IIIb, and IIIc accounting for 49.2%, 31.1%, and 19.7%, respectively. These findings suggest that advanced histopathological injury at diagnosis is common in pediatric specialty-center cohorts, although the exact proportions vary by case mix, diagnostic pathway, and biopsy denominator.

Several pediatric studies have likewise reported no significant association between endoscopic markers and histopathological severity. For example, Semwal *et al.*,^[15] found that scalloping and mucosal nodularity had poor predictive accuracy for Marsh grade, mirroring our results. Similarly, multicenter data from North America and Europe have shown that endoscopic abnormalities lack sufficient specificity and sensitivity to reliably predict villous atrophy severity. These data collectively reinforce that endoscopic markers alone are insufficiently sensitive or specific to replace duodenal biopsy in children.^[16,17]

On the other hand, a few pediatric cohorts have reported significant associations between endoscopy and histology. These discrepancies may be explained by methodological differences, including larger sample sizes, more extensive biopsy sampling, and variations in disease distribution. Patchy mucosal involvement in pediatric CD may also obscure true associations, particularly when too few biopsies are obtained or specimen orientation is suboptimal. Differences in age distribution at presentation and variability in clinical practice – both endoscopic and pathological – further contribute to inconsistencies across studies.

Clinical implications

The observed numerical patterns remain clinically informative. Scalloping, duodenal mucosal changes, and nutritional deficiencies were more frequent in patients with higher Marsh grades, suggesting potential value as supportive indicators during diagnostic evaluation. However, these markers cannot substitute for biopsy, reaffirming the central role of histology in the pediatric diagnostic pathway.

The high frequency of severe Marsh III lesions and associated nutritional or autoimmune comorbidities suggests that many

children had advanced disease features at diagnosis; however, because the diagnostic interval was not collected, the reasons for this pattern cannot be determined.

Limitations

This study has several limitations. First, the single-center design may introduce center-specific referral and practice patterns. Second, the retrospective data collection and reliance on medical records may have resulted in missing or incomplete documentation, particularly for EMA results and detailed clinical symptomatology. Third, the high proportion of missing EMA results may reduce diagnostic completeness and limit external validity, especially when comparing our cohort with centers that routinely use complete serologic confirmation or non-biopsy diagnostic algorithms. Fourth, the sample size ($n = 58$) limited the power to detect moderate associations between clinical, endoscopic, and histopathological variables. In addition, no correction for multiple comparisons was applied; therefore, the analyses should be considered exploratory and interpreted cautiously. Fifth, the study lacked longitudinal follow-up after gluten-free diet initiation, limiting evaluation of symptom resolution, serological response, or histopathological recovery. In addition, the study did not capture the diagnostic interval (e.g., time from symptom onset, first healthcare contact, or referral to confirmed diagnosis), so no temporal or causal conclusions can be drawn regarding delayed diagnosis.

These factors may limit applicability to other pediatric populations and healthcare settings. Future multicenter prospective studies with larger cohorts, more complete serological documentation, and post-gluten-free diet follow-up are warranted to validate and expand upon these findings.

Taken together, the predominance of severe Marsh III lesions, frequent nutritional deficiencies, and coexisting autoimmune disorders suggests that many patients had advanced disease features at diagnosis. However, no conclusions about diagnostic delay can be drawn because the diagnostic interval was not assessed.

CONCLUSION

This study highlights the heterogeneous clinical presentations, strong tTG-IgA seropositivity, and predominance of advanced histopathological changes among pediatric patients with CD. In this tertiary referral setting, biopsy-confirmed pediatric CD frequently presented with advanced mucosal injury despite heterogeneous clinical symptoms. Although endoscopic abnormalities such as scalloping and gastritis were frequently observed, they did not significantly correlate with histological severity, underscoring the indispensable role of duodenal biopsy in diagnosis. Nutritional deficiencies and autoimmune comorbidities were common, reflecting the

systemic impact of the disease. From a clinical standpoint, these findings reaffirm that histopathological confirmation remains essential for accurate diagnosis and disease staging, even in patients with strong serological evidence or typical endoscopic features. These patterns indicate advanced mucosal and systemic disease features at diagnosis; however, diagnostic timing was not assessed, and no conclusions can be drawn regarding diagnostic delay.

Author contributions: AA: Conceptualization, methodology, investigation, data curation, writing – original draft and supervision; HI: Conceptualization, methodology, formal analysis, writing – review and editing; MAF: Investigation, histopathological analysis, validation, writing – review and editing; A.Ao.: Investigation, histopathological analysis, validation, writing – review and editing; MAK: Investigation, data acquisition, writing – review and editing; AAl: Investigation, data acquisition, writing – review and editing; WA: Investigation, data acquisition, writing – review and editing; MAIm: Investigation, data acquisition, writing – review and editing; MAIh: Investigation, data acquisition, writing – review and editing; WAm: Investigation, data acquisition, writing – review and editing. All authors read and approved of the final manuscript.

Ethical approval: The research/study was approved by the Institutional Review Board at King Saud Medical City, number H-01-R-053, dated August 2025.

Declaration of patient consent: Patient's consent is not required as patient's identity is not disclosed or compromised.

Financial support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

Availability of data and material: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: Artificial intelligence tools were used only for language editing. No AI tool was used to generate scientific content, analyze data, interpret results, or draw conclusions. All substantive intellectual contributions were made solely by the authors.

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