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Original Article

Coeliac Disease in Children with Hepatic Dysfunction: Clinical, Serological, and Histopathological Correlation in a Tertiary Care Hospital of Bangladesh

Parveen S[1], *Safiullah ABM[2], Helal MA[3], Rahman MA[4], Chowdhury MS[5], Chowdhury MFK,[6] Rahman MZ[7]

Abstract:

Coeliac disease (CD) is an immune-mediated enteropathy increasingly recognized with extraintestinal manifestations, including hepatic dysfunction. This study aimed to determine the frequency of CD among children with hepatic dysfunction and to evaluate their demographic, clinical, biochemical, serological, endoscopic, and histopathological characteristics. This cross-sectional study was conducted among children aged 1–18 years presenting with persistent hepatic dysfunction after exclusion of established liver diseases. Of 67 eligible children, 62 were finally included. All underwent serum IgA anti-tissue transglutaminase (anti-tTG) testing, and seropositive children subsequently underwent upper gastrointestinal endoscopy with duodenal biopsy. Histopathological grading was performed according to the Marsh classification. Statistical analyses included chi-square test, Fisher's exact test, independent-s amples t-test, odds ratio (OR), 95% confidence interval (CI), and p-values. Among the 62 children, 22 (35.5%) were anti-tTG positive, while biopsy findings compatible with CD were identified in 19 seropositive children, representing 30.6% of the total study population. The mean age of seropositive children was 10.30 ± 4.10 years; 68.2% were male, 81.8% were urban residents, and 63.6% belonged to middle-income families. Chronic diarrhea was present in all children, whereas abdominal distension was significantly more common among seropositive cases (p=0.002). Failure to thrive, anorexia, pallor, and muscle wasting were more frequent among seropositive children. Mean haemoglobin level was significantly lower in seropositive children (p<0.001), confirming anaemia as a major extraintestinal manifestation. Raised serum glutamic-pyruvic transaminase (SGPT) was observed in 72.7% of seropositive children, with significantly higher mean SGPT levels compared with seronegative children (p=0.024), supporting the association between CD and hepatic dysfunction. Endoscopic abnormalities included scalloping of mucosal folds (36.4%), loss of duodenal folds (13.6%), and mosaic mucosal appearance (4.5%), although 45.5% had normal endoscopic appearances. Histopathology revealed Marsh 3a lesions in 63.2%, Marsh 3b in 21.1%, and Marsh 3c in 15.8% of biopsy-compatible cases. Increasing Marsh severity was associated with lower haemoglobin and albumin levels and higher bilirubin, SGPT, and INR values. More than one-third of children with hepatic dysfunction were anti-tTG positive, and most seropositive children had biopsy-compatible CD. Routine serological screening may help identify a treatable cause of paediatric hepatic dysfunction.

Keywords: *Coeliac disease, hepatic dysfunction, tissue transglutaminase, distal part of duodenum*

1. Dr. Shohely Parveen, Associate Professor, Department of Paediatrics, Bangladesh Medical University (BMU), Shahbag, Dhaka. Email: shohelypaediatrics@yahoo.com.
2. *Dr. ABM Safiullah, Associate Professor, Department of Gastroenterology, BMU, Shahbag, Dhaka. Email: gastroshafi67@gmail.com
3. Dr. Md Al Helal, DCH, Assistant Professor, Department of Paediatrics, BMU.
4. Dr. Mohammad Asadur Rahman, Associate Professor, Department of Gastroenterology, BMU, Shahbag, Dhaka.
5. Dr. Mohammad Shoaib Chowdhury, Associate Professor, Department of Gastroenterology, BMU, Shahbag, Dhaka.
6. Dr. Md. Fazlul Karim Chowdhury, Assistant Professor, Department of Gastroenterology, BMU, Shahbag, Dhaka.
7. Dr. Md. Zahidur Rahman, Professor, Department of Gastroenterology, BMU, Shahbag, Dhaka.

*For correspondence

INTRODUCTION

Coeliac disease (CD) is a chronic immune-mediated systemic disorder triggered by dietary gluten in genetically susceptible individuals and characterized by small intestinal mucosal inflammation, crypt hyperplasia, and villous atrophy.[1,2] Although once considered primarily a gastrointestinal disease of infancy, CD is now recognized as a multisystem disorder with diverse intestinal and extraintestinal manifestations occurring at any age.[3,4] Global epidemiological studies estimate the pooled prevalence of CD to be approximately 1%, with rising detection rates in both developed and developing countries.[5,6] In South Asia, including Bangladesh, increasing awareness and wider availability of serological

testing have contributed to improved recognition of pediatric CD.[7,8]

The clinical presentation of CD has evolved considerably over recent decades. Classical manifestations such as chronic diarrhea, abdominal distension, weight loss, and failure to thrive are now less common, whereas non-classical and extraintestinal presentations are increasingly encountered.[9,10] These include iron deficiency anemia, short stature, delayed puberty, metabolic bone disease, neurological disorders, endocrine abnormalities, and hepatobiliary involvement.[11,12] Hepatic dysfunction is an important extraintestinal manifestation and may occasionally represent the sole clinical presentation of CD.[13]

Liver involvement associated with CD ranges from isolated asymptomatic elevation of liver enzymes to chronic liver disease and autoimmune hepatobiliary disorders.[14,15] Mild hypertransaminasaemia, often termed "hepatitis," is the most frequently reported hepatic abnormality and may normalize following institution of a gluten-free diet.[16,17] The mechanisms underlying hepatic injury are not fully understood but are thought to involve increased intestinal permeability, immune-mediated hepatocellular injury, chronic systemic inflammation, nutritional deficiencies, and autoimmune processes.[18,19] Enhanced intestinal permeability may facilitate translocation of toxins, antigens, and inflammatory mediators into the portal circulation, contributing to hepatic inflammation and injury.[20]

Several studies have demonstrated significant associations between CD and autoimmune liver diseases, including autoimmune hepatitis, primary sclerosing cholangitis, and autoimmune cholangitis.[21,22] CD has also been identified in children with cryptogenic liver disease, nonalcoholic fatty liver disease, and advanced chronic liver disease.[23,24] Conversely, the prevalence of CD among children with unexplained hepatic dysfunction is substantially higher than that in the general population.[25,26] Early recognition is therefore clinically important because prompt initiation of a gluten-free diet may lead to normalization of liver enzymes, improvement in nutritional status, prevention of complications, & avoidance of unnecessary investigations.[27,28]

Diagnosis of CD is based on clinical suspicion, serological testing, and histopathological confirmation. Measurement of immunoglobulin A (IgA) anti-tissue transglutaminase antibody (anti-tTG) is the preferred initial screening test because of its high sensitivity and specificity.[29,30] Upper gastrointestinal endoscopy with duodenal biopsy remains the standard confirmatory investigation, particularly in atypical cases.[31] Histological changes are graded using the modified Marsh classification according to the degree of intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy.[32] Current ESPGHAN guidelines recommend targeted screening for CD among high-risk groups, including children with unexplained hepatic dysfunction.[33]

Despite increasing recognition, CD remains under-diagnosed in many developing countries because of limited awareness and restricted access to diagnostic facilities. Data regarding the frequency and clinicopathological characteristics of CD among Bangladeshi children with hepatic dysfunction are still limited. Therefore, this study was undertaken to determine the frequency of CD among children presenting with hepatic dysfunction and to evaluate their clinical, serological, and histopathological characteristics.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Pediatrics in collaboration with the Department of Gastroenterology and Hepatology, Bangladesh Medical University, Dhaka, Bangladesh, over 18 months from January 2022 to June 2023. The study aimed to determine the frequency of CD among children presenting with hepatic dysfunction and to evaluate their clinical, serological, and histopathological characteristics.

Children aged 1–18 years with hepatic dysfunction were enrolled consecutively using a non-probability consecutive sampling technique. Hepatic dysfunction was defined as persistent elevation of serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels above the upper normal limit for more than three months, with or without clinical evidence of liver involvement. Initially, 67 eligible children were assessed; 3 were excluded because of contraindications to upper gastrointestinal endoscopy, and 2 declined consent for biopsy. Finally, 62 children were included in the analysis.

Children with known chronic liver disease of established etiology, including viral hepatitis, Wilson disease, autoimmune hepatitis, metabolic liver disorders, drug-induced liver injury, congestive hepatopathy, malignancy, previously diagnosed disease, or those already on a gluten-free diet were excluded.

A detailed history and physical examination were performed using a predesigned semi-structured questionnaire. Demographic characteristics, presenting complaints, bowel habits, abdominal symptoms, jaundice, anorexia, weight loss, growth failure, family history, and associated autoimmune conditions were recorded. Anthropometric measurements and clinical examination for hepatomegaly, splenomegaly, ascites, edema, pallor, and signs of chronic liver disease were conducted.

Baseline investigations included complete blood count, erythrocyte sedimentation rate, serum bilirubin, ALT, AST, alkaline phosphatase, serum albumin, prothrombin time, and international normalized ratio. Additional investigations, such as viral markers, serum ceruloplasmin, autoimmune markers, slit-lamp examination for Kayser–Fleischer rings, and abdominal ultrasonography were performed where indicated to exclude other causes of hepatic dysfunction.

All enrolled children underwent serological screening for disease by measurement of serum immunoglobulin A (IgA) anti-tissue transglutaminase antibody (anti-tTG) using enzyme-linked immunosorbent assay (ELISA). Anti-tTG IgA levels >10 U/mL were considered positive. Total serum IgA was measured in selected clinically suspected cases with negative anti-tTG results to exclude selective IgA deficiency.

Children with positive anti-tTG serology underwent upper gastrointestinal endoscopy under appropriate sedation after obtaining written informed consent. At least four biopsy samples were obtained from the second part of the duodenum and one from the duodenal bulb. Specimens were fixed in 10% buffered formalin and examined histopathologically by experienced histopathologists blinded to serological findings. Histological grading was performed according to the modified Marsh classification system. Marsh grade I or higher lesions with positive serology were considered compatible with disease.

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, while qualitative variables were expressed as frequency and percentage. Group comparisons were performed using an independent sample t-test, Mann–Whitney U test, Chi-square test, or Fisher's exact test as appropriate. A p-value <0.05 was considered statistically significant.

Ethical approval was obtained from the Institutional Review Board of Bangladesh Medical University. Written informed consent was obtained from parents or legal guardians, and confidentiality was maintained throughout the study.

RESULTS

The demographic characteristics of the 62 children involved in the study are summarized through variables, age group, mean age, sex, residence, socioeconomic status, and family history of disease. The data were directly extracted from the RCT study dataset. The mean age, along with the standard deviation [SD], was 9.4 ± 3.8 years. The age distribution showed that 30.7% of the children were in <5 - 9 years, 45.2% in the 10 - 14 years, and 24.2% were in the 15- 18 years age group. Males comprised 69.4% of the sample, and the male-to-female ratio was 2.26:1. Children residing in urban areas was 82.3%, whereas, according to their socioeconomic status, 27.4% was in the low-income group, 58.1% in the middle-income, and 14.5% in the high-income group. Notably, none of the children had a family history of disease.

Figure 1 illustrates the diagram of the study flow and seropositive subgroup analysis. A total of 67 children with hepatic dysfunction were initially evaluated for eligibility throughout the study period. Among these, 3 children were excluded due to contraindications for upper gastrointestinal endoscopy, while 2 opted out of consent for endoscopic biopsy. Ultimately, 62 children were included in the final analysis and were screened for IgA anti-tissue transglutaminase (anti-tTG). Anti-tTG positive was found in 22 children (35.5%) and negative in 40 (64.5%). Of the 22 seropositive children who later

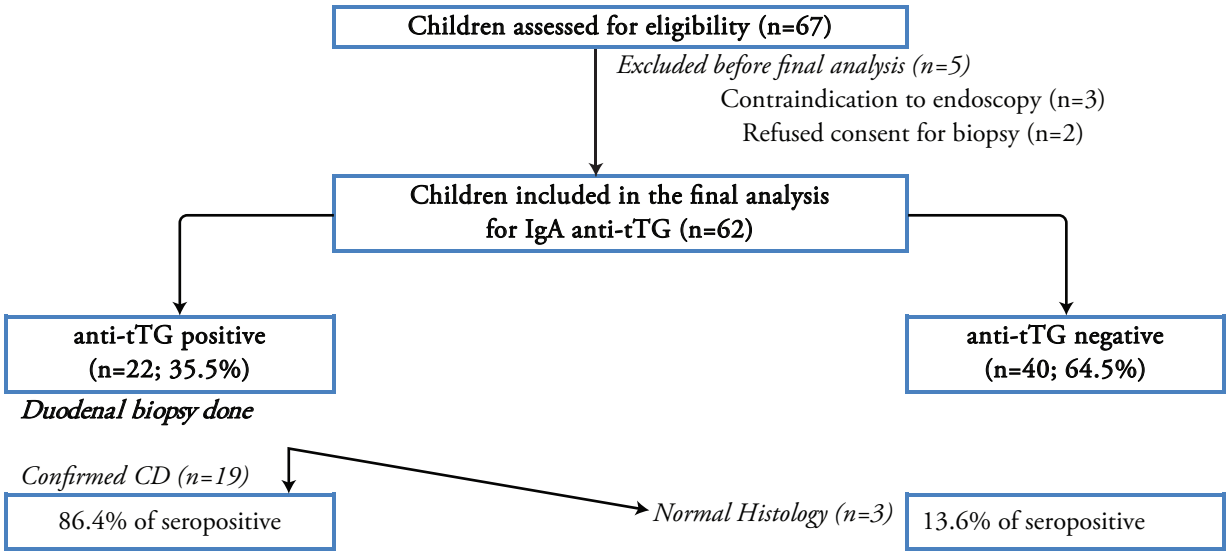


Figure 1: Diagram of Study Flow and Seropositive Subgroup Analysis

underwent duodenal biopsy, histologically confirmed disease (CD) was identified in 19 (86.3%) cases, with normal histology observed in 3 (13.7%) instances.

Table I details the demographic characteristics of seropositive children. The mean age (mean ± SD) of the children was 10.30 ± 4.10 years; 50.0% of seropositive children belonged to the 10-14 years age group (50.0%), followed by 5-9 years (22.7%). Male children constituted 68.2% of the seropositive group. Urban residents were 18 (81.8%), and 14 (63.6%) from middle-income households, followed by 6 (27.3%) from low-income households. Family history of disease was absent in all anti-tTG-positive children.

Table I: Demographic characteristics of seropositive children (n=22)

Variable	n (%)
Age group, years	
<5	2 (9.1)
5-9	5 (22.7)
10-14	11 (50.0)
15-18	4 (18.2)
Age, mean ± SD	10.30 ± 4.10
Sex	
Male	15 (68.2)
Female	7 (31.8)
Residence	
Urban	18 (81.8)
Rural	4 (18.2)
Socioeconomic status	
Low	6 (27.3)
Middle	14 (63.6)
High	2 (9.1)

Family history of disease Table II shows the comparison of the mean age between seropositive and seronegative children. The mean difference between the anti-tTG-positive and negative children was calculated using an independent-sample t-test, revealing a statistically significant difference ($p < 0.05$). The 95% confidence interval (CI) for the mean difference was estimated using pooled variance.

Table II: Comparison of Mean Age between Seropositive and Seronegative Children (n=62)

Group	Mean Age ± SD (years)	Mean Difference	95% CI	p-value
Positive (n=22)	10.3 ± 4.1	3.8 years	1.2-6.4	<0.05
Negative (n=40)	6.5 ± 4.5	—	—	—

The 95% confidence interval (CI) for the mean difference was estimated using pooled variance.

Table III shows the association of clinical symptoms with anti-tTG seropositivity. Chronic diarrhea was present in all children (100%), and abdominal pain/discomfort had a higher prevalence (36.4% vs. 42.5%) in both seropositive and seronegative groups, though this was not statistically significant at $p < 0.05$. The prevalence of abdominal distension (38.1% vs. 5.1%) was also significantly higher in seropositive cases ($p = 0.002$). Other symptoms, such as failure to thrive (31.8%), anorexia (22.7%), and fever (22.7%), were more prevalent in the seropositive group, while fatigue (18.2% vs. 17.5%) was almost similar across both groups. Short stature, vomiting, and weight loss were almost equally distributed at a lower rate across the groups, but muscle wasting was not detected in the seronegative group.

Table III: Association of Clinical Symptoms with Anti-tTG Seropositivity (n=62)

Clinical symptom	Seropositive (%)	Seronegative (%)	Fisher's exact p
Chronic diarrhea	100.0%	100.0%	1.000
Abdominal pain/discomfort	36.4%	42.5%	0.788
Anorexia	22.7%	5.0%	0.086
Fatigue	18.2%	17.5%	1.000
Short stature	9.1%	7.7%	1.000
Muscle wasting	4.5%	0.0%	0.355
Failure to thrive	31.8%	10.3%	0.079
Fever	22.7%	10.0%	0.259
Vomiting	9.1%	10.0%	1.000
Abdominal distension	38.1%	5.1%	0.002
Weight loss	4.5%	5.0%	1.000

Fisher's exact test was applied for small cell counts; p-values are exact. Statistically significant differences = $p < 0.05$.

Table IV presents the comparison of mean levels of laboratory parameters between seropositive and seronegative children. The mean haemoglobin level was significantly lower in seropositive children ($p < 0.001$). SGPT was significantly higher in seropositive children ($p = 0.024$). Bilirubin, INR, and Albumin showed mild differences but were not statistically significant.

Table IV: Comparison of Mean Levels of Laboratory Parameters by AntitTG Status (n=62)

Parameter	AntitTG Positive (n=22)	AntitTG Negative (n=40)	Mean Difference	95% CI	p value
Haemoglobin (g/dL)	9.6 ± 1.14	11.7 ± 1.47	−2.1	−2.77 to −1.43	< 0.001
Bilirubin (mg/dL)	1.3 ± 0.7	1.1 ± 0.5	+0.2	−0.1 to +0.5	0.18
SGPT (U/L)	84.2 ± 28.6	68.5 ± 25.1	+15.7	+2.1 to +29.3	0.024
INR	1.2 ± 0.3	1.1 ± 0.2	+0.1	−0.02 to +0.22	0.09
Albumin (g/dL)	3.8 ± 0.5	4.0 ± 0.4	−0.2	−0.5 to +0.1	0.12

Independent sample t-tests were applied; values are expressed as mean ± SD. Confidence intervals (CI) are shown for mean differences. Statistically significant differences = $p < 0.05$. INR =International Normalized Ratio.

Table V contains the clinical and endoscopic profile of anti-tTG-positive children. Among the 22 anti-tTG-positive children, the hepatic or biochemical presentations recorded were raised SGPT, hypo- albuminaemia, coagulopathy, and hyperbilirubinaemia. Endoscopy was normal in 10 children (45.5%); abnormal endoscopic findings comprised mosaic duodenal mucosa in 1 (4.5%), scalloping of mucosal folds in 8 (36.4%), and loss of duodenal folds in 3 (13.6%).

Table V: Clinical and Endoscopic Profile of Anti-tTG-positive Children (n=22)

Finding	n (%)
Clinical Findings	
Raised SGPT	16 (72.7)
Hypoalbuminaemia	1 (4.5)
Coagulopathy	1 (4.5)
Hyperbilirubinaemia	4 (18.2)
Endoscopic Findings	
Normal endoscopic appearance	10 (45.5)
Mosaic duodenal mucosa	1 (4.5)
Scalloping of mucosal folds	8 (36.4)
Loss of duodenal folds	3 (13.6)

Figure 2 displays the distribution of biopsy findings according to the modified Marsh classification among anti-tTG positive children. Of the 22 seropositive children who underwent histopathological evaluation, 19 demonstrated biopsy features compatible with disease. Marsh type 3a was the most frequent histological pattern (63.16%), followed by Marsh type 3b (21.05%) and Marsh type 3c (15.79%). Conversely, 3 seropositive children had normal histology.

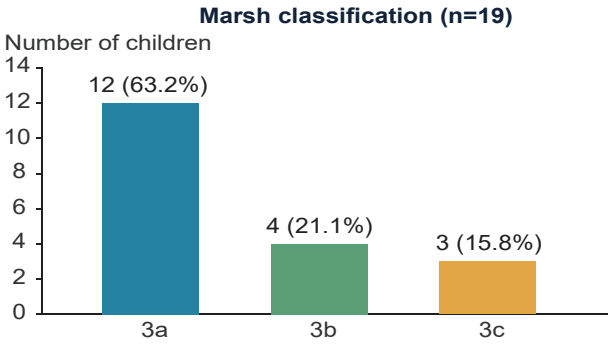


Figure 2: Marsh Classification in children compatible with biopsy (n = 19)

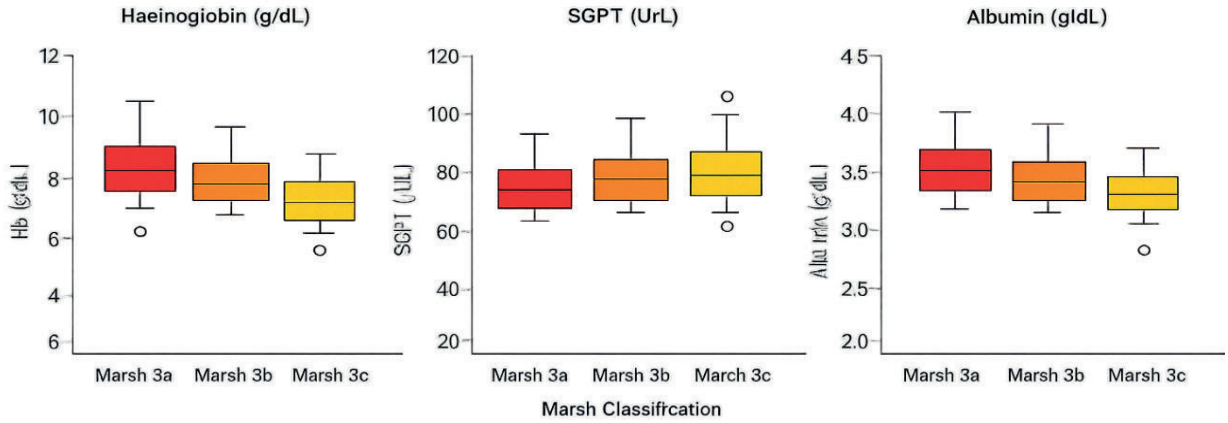
Table VI demonstrates the laboratory trends among seropositive children according to Marsh classification. Mean haemoglobin and albumin levels progressively decreased from Marsh 3a to Marsh 3c, whereas bilirubin, SGPT, and INR values increased with higher Marsh grades.

Table VI: Trends and Implications of Laboratory Parameters of Seropositive Children by Marsh Classification (n = 19)

Parameter	Trend Across Marsh Grades (Mean Level±SD)	Clinical Consequence
Hb	↓ **3a** (9.7±1.1) →**3b** (9.3±1.0) →**3c** (8.8±0.9)	Progressive anemia due to malabsorption
Bilirubin	↑ **3a** (1.2±0.6) →**3b** (1.4±0.7) →**3c** (1.6±0.8)	Worsening hepatic dysfunction
SGPT	↑ **3a** (82.5±27.8) →**3b** (88.2±30.5) →**3c** (94.6±32.1)	Increased hepatocellular injury
INR	↑ **3a** (1.1 ± 0.2) →**3b** (1.2 ± 0.3) →**3c** (1.3 ± 0.3)	Reduced hepatic synthetic capacity
Albumin	↓ **3a** (3.9 ± 0.4) →**3b** (3.7 ± 0.5) →**3c** (3.5 ± 0.6)	Nutritional compromise and chronic inflammation

Abbreviations: SGPT, serum glutamic-pyruvic transaminase.

Figure 3 shows the distribution of haemoglobin, SGPT, and albumin levels according to Marsh classification among biopsy-compatible cases. Progressive reduction in haemoglobin and albumin levels and elevation of SGPT were observed with increasing histological severity. These box plots serve as a visual complement to Table VI.



These box plots are intended to visually enhance the information presented in Table VI.
Abbreviations: SGPT, serum glutamic-pyruvic transaminase.

Figure 3: Boxplots of Haemoglobin, SGPT, and Albumin Levels Across Marsh Grades in Seropositive Children (n=19)

DISCISSION

This study demonstrated a substantial burden of CD among children presenting with hepatic dysfunction at a tertiary-care referral centre in Bangladesh. Among 62 enrolled children, 22 were seropositive for anti-tTG IgA, yielding a seropositivity rate of 35.5%. Histopathological changes compatible with disease were identified in 19 of the 22 seropositive children (86.4%), representing 30.6% of all screened participants. Similar associations between CD and cryptogenic liver dysfunction, hyper-transaminasaemia, and autoimmune hepatobiliary disorders have been reported previously.[1–3,11–15]

The prevalence observed in this study was considerably higher than that reported in general paediatric populations, which is expected because only children with hepatic dysfunction were included. Global studies estimate the prevalence of the CD at approximately 1% in the general population, with higher rates among selected risk groups.[4–6] Asian and South Asian studies have similarly highlighted increasing recognition of atypical and extraintestinal presentations of CD.[7–9] The present findings therefore support targeted screening among children with unexplained hepatic dysfunction. Raised SGPT was observed in 72.7% of seropositive children, supporting the concept of " hepatitis," which may improve following gluten withdrawal.[15–17]

The demographic profile showed that seropositive children had a significantly higher mean age than seronegative children (10.30 ± 4.10 years versus a lower mean age in the seronegative group), with half belonging to the 10–14-year age group. This suggests delayed diagnosis in Bangladeshi children compared with Western populations, where diagnosis often occurs before 2 years of age.[23] Comparable South Asian studies have reported diagnosis at older ages ranging from 6.3 to 8.6 years.[12] Male predominance (68.2%) was observed, alongside predominance of urban residence (81.8%) and middle-income socioeconomic status (63.6%). Although CD is generally reported more commonly in females, similar variations in sex distribution have been described in hospital-based regional cohorts.[8,10,11]

Regarding clinical manifestations, chronic diarrhea was present in all children irrespective of serological status, indicating that it was a common symptom among children with hepatic dysfunction overall. However, abdominal distension was significantly more common in seropositive children (p=0.002), suggesting greater diagnostic relevance. Failure to thrive, anorexia, pallor, and muscle wasting were also more frequent among seropositive children. Similar observations have been reported in South Asian studies where abdominal distension and growth failure were strongly associated with paediatric CD.[12,21] European studies have additionally demonstrated a shift toward atypical manifestations such as anaemia, anorexia, and fatigue.[9,10] The presence of muscle wasting exclusively among seropositive children may indicate more advanced malabsorption and nutritional compromise.

Anaemia emerged as a major associated finding. Mean haemoglobin was significantly lower among seropositive children (p<0.001), supporting previous evidence that iron deficiency anaemia is a common extraintestinal manifestation of CD due to impaired proximal intestinal absorption.[11,22] Liver enzyme abnormalities were also prominent. SGPT levels were significantly higher among seropositive children (p=0.024), consistent with earlier studies describing mild-to-moderate hyper-transaminasaemia in untreated CD.[14–16] Other biochemical parameters, including bilirubin, INR, and albumin, showed non-significant differences. European and South Asian studies have similarly identified elevated liver enzymes and anaemia as common abnormalities in atypical paediatric CD.[12,13,15,21]

Endoscopic findings among seropositive children included scalloping of duodenal folds, loss of folds, and mosaic mucosal appearance. However, nearly half of the seropositive children demonstrated normal endoscopic appearances, emphasizing that normal endoscopy does not exclude CD. Previous studies likewise reported subtle or absent macroscopic abnormalities despite significant histological injury.[17–20] Therefore, duodenal biopsy remains essential in suspected cases even when endoscopic findings appear normal.

Histopathological evaluation showed Marsh 3a lesions as the most frequent abnormality (63.2%), followed by Marsh 3b (21.1%) and Marsh 3c (15.8%). Similar predominance of Marsh 3a lesions has been reported in paediatric cohorts.[28–32] Three anti-tTG-positive children demonstrated normal histology, possibly reflecting potential disease, patchy mucosal involvement, or early-stage disease.[24,26,30] Such children require close follow-up because serological positivity may precede overt villous atrophy.

Another important observation was the progressive deterioration of laboratory parameters with increasing Marsh severity. Children with Marsh 3c lesions had lower haemoglobin and albumin levels, together with higher bilirubin, SGPT, and INR values, compared with those with Marsh 3a lesions. Boxplot analyses similarly demonstrated declining haemoglobin and albumin and rising SGPT levels with increasing histological severity. South Asian cohorts similarly describe progressive biochemical derangements with higher Marsh grades, linking anaemia and hypoalbuminaemia to malabsorption and chronic inflammation[12,21]. The incremental rise in INR and bilirubin in our cohort parallels reports of impaired hepatic synthetic capacity in advanced CD, though these changes are less consistent across studies[13,15]. These findings suggest that greater intestinal mucosal injury may correlate with worsening nutritional status and hepatic dysfunction, strengthening the biological plausibility of the association between CD severity and liver involvement.

LIMITATIONS

It was a single-centre descriptive cross-sectional study conducted at a tertiary-care hospital, which may limit generalizability to the wider paediatric population of Bangladesh. The sample size was relatively modest, and selection bias may have occurred because children attending tertiary centres often represent more severe or persistent cases.

CONCLUSIONS

In this study, anti-tTG seropositivity was identified in 35.5% of screened children, while biopsy-compatible CD was confirmed in 30.6%. Seropositive children demonstrated significantly lower haemoglobin levels and frequent liver enzyme abnormalities, while laboratory derangements intensified with increasing Marsh severity. Normal endoscopic appearance did not exclude histopathological CD, emphasising the importance of biopsy confirmation. Routine anti-tTG screening should therefore be considered in children with persistent unexplained hepatic dysfunction, irrespective of sex or classic gastrointestinal symptoms.

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