



# Assessment of the Predictive Factors Influencing the Diagnosis and Severity of Villous Atrophy in Patients with Celiac Disease and Iron Deficiency Anemia Referred for Diagnostic Endoscopy in Basrah, Iraq

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## Abstract

**Background:** The classic celiac disease (CD) presentation in individuals with iron deficiency anemia (IDA) has been changed given the large percentage of subtle or asymptomatic cases. The study objective was to assess the predictive factors influencing the diagnosis and severity of villous atrophy in individuals with CD and IDA referred for a diagnostic endoscopy.

**Methods:** This was a retrospective observational, cross-sectional analysis of the medical records of 499 individuals with IDA in 2 centers in Basrah, Iraq, who referred for possible diagnosis of CD within 10 years (2006-2016). The relationship of the severity of anemia, demographic characteristics, symptomatology, and celiac serological results on the final diagnostic endoscopic evaluation was evaluated using a univariate analysis, at a P value  $\leq 0.05$ . The study adopted the Marsh classification for celiac disease diagnosis where Marsh type 3 represents the definite celiac disease.

**Results:** The definite diagnosis was seen in 44.5% of the cohort (n = 222), with asymptomatic cases representing 22.5% of cases (n = 50). The mean age was (27  $\pm$  11) years, with significant association to (female gender, age  $\leq 45$  years, positive celiac serology, and severity of anemia). After adjustment of the variables, the Marsh type was significantly correlated with positive celiac serology, low hemoglobin, and presence of gastrointestinal symptoms.

**Conclusion:** The positive celiac serology, low hemoglobin  $< 9$  g/L, and the presence of gastrointestinal symptoms are strong predictors of the severity of villous atrophy (Marsh type).

**Keywords:** Anemia, Anti-Tissue, Celiac, Endoscopy, Gastrointestinal, Marsh, Serology, Symptoms

**Conflicts of Interest:** None declared

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## Introduction

Celiac disease (CD) is a common enteropathy due to permanent gluten sensitivity in genetically sensitive people under immune-mediated mechanisms (1, 2), which usually causes recurrent diarrheal episodes with longer duration of anemia than those without CD (3, 4). It is increasingly recognized among the elderly (5, 6), with a

different subtle or quite troubling symptoms (7). Similar to other autoimmune disorders, CD occurs more frequently in women (7-9). Its incidence rate continues to rise until the sixth decade of life after which it decreases in women and gradually rise in men (7).

The gold standard test for the CD diagnosis is small

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### ↑What is “already known” in this topic:

A percentage of patients with celiac disease and iron deficiency may have no symptoms which are related to the digestive system.

### →What this article adds:

The predictability of severity of villous atrophy in patients with celiac disease and iron deficiency anemia is augmented by the positive celiac immune serology in patients with gastrointestinal symptoms and marked reduction of hemoglobin below 9 g/L.

bowel mucosal biopsies (SBBx), which is recommended in individuals with iron deficiency anemia (IDA). These biopsies should be guided by serology and endoscopic visualization (6,10), which should include random gastric antral and fundal biopsies and duodenal biopsies to assess the causative pathology (4, 11). The diagnosis is pathologically based, with a degree of clinical-histologic and clinical-biochemical discrepancy in suspected patients; a “normal” endoscopic appearance on biopsy is not sufficient to exclude CD (12, 13).

The classic presentation of CD is chronic diarrhea, malabsorption, and weight loss, yet, the treating physicians frequently encounter asymptomatic patients with atypical forms of CD, who did not seek medical advice earlier (1, 5, 8).

This study aims to assess the predictive factors influencing the diagnosis and severity of villous atrophy in patients with CD and IDA who were referred for diagnostic endoscopy in Basrah, Iraq.

**Methods**

This was a retrospective observational cross-sectional analysis of the hospital medical records of 499 individuals with IDA, who were referred to As-Sadr and Faihaa Teaching hospitals, for possible diagnosis of CD during January 2006 and January 2016).

Medical data from (endoscopy, histopathology, laboratory units) from both hospitals were evaluated. We illustrated the evaluation algorithm in Figure 1, with our enrollment criteria (14, 15).

The hemoglobin (Hb) level, serum ferritin, serum iron, mean corpuscular volume (MCV), total iron-binding capacity (TIBC), and the transferrin saturation (TS) were recorded. Also, 75% of enrolled patients (n = 374) were tested for celiac serology. We tabulated our medical data according to the following criteria:

- Demographic and general characteristics
- Duration of hospital stay for inpatients
- Celiac serological tests: anti-tissue transglutaminase IgA (ATTGA) and IgG (ATTGG) subtypes
- Findings of gastrointestinal (GI) endoscopic biopsy
- The criteria of IDA severity are as follows (14):
  - Criteria of severe IDA are Hb<9 g/L, serum iron <15 µg/dL, serum ferritin <9 µg/L, MCV <70 fL, TIBC >400 µg/dL, and TS <3.5%.
  - Criteria of mild to moderate IDA are Hb 9–13 g/L, serum ferritin 9-15 µg/L, serum iron 15-30 µg/dL, MCV 70–90 fL, TIBC 360-400 µg/dL, and TS 3.5-10%.

The biopsy-proven CD was confirmed if the SBBx revealed Marsh type 3 (A, B, and C), which includes crypt hyperplasia, increased intraepithelial lymphocytes, along

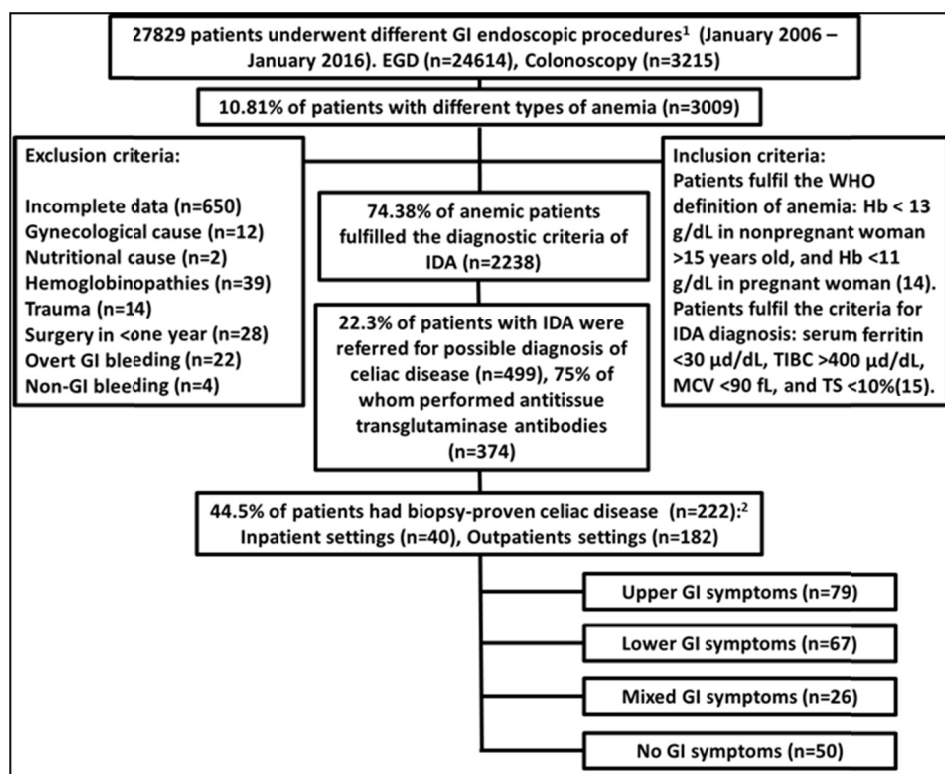


Fig. 1. A flow chart illustrated the algorithm of the study for the 499 patients with IDA who were referred for a possible diagnosis of CD. The endoscopic diagnostic yield for CD is 222/499 patients (44.49%).

CD, celiac disease; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; Hb, hemoglobin; IDA, iron deficiency anemia; Ig, immunoglobulin; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; TS, transferrin saturation; WHO, World Health Organization.

<sup>1</sup> All procedures utilized the Pentax Medical (HOYA Group-Shinjuku-Tokyo) or Olympus (Olympus Surgical Technologies America-Southborough-MA) endoscopic system.

<sup>2</sup> Only three patients had a colonoscopy (one man and two women) and revealed lower GI malignancy.

with villous atrophy (partial: 3A, subtotal: 3B, and total: 3C) (6).

The analysis included 4 categories of GI symptoms:

- Upper GI symptoms included dysphagia, nausea, vomiting, heartburn, upper abdominal pain, and whether they were relieved by food or antacids.

- Lower GI symptoms included any changed bowel habit towards constipation or diarrhea, and any severity of lower abdominal colic.

- Asymptomatic was the term used to describe the IDA patients without GI symptoms.

- Patients with mixed lower and upper GI symptoms.

The estimation of the ATTGA and ATTGG was done by the enzyme-linked immunosorbent assay technique (ELISA) (Aeskulisa tTg-A and Aeskulisa tTg-G) (BioTek ELx800, and Alegria, ORGENTEC Diagnostika). A value  $> 10$  U/mL for ATTGA and  $> 9$  U/mL for ATTGG was considered positive. A value  $< 4$  U/mL for ATTGA and  $< 6$  U/mL for ATTGG was considered negative. The values between the positive and negative results were considered weak positive.

Ethical approval for data access was obtained. Data were entered and then analyzed on IBM SPSS Statistics for Windows, Version 23.0. The study used the mean  $\pm$  standard deviation (SD) and frequency (%) for the expression of the data. We used the analysis of variance (ANOVA), general univariate analysis, and multinomial logistic regression analysis to assess for possible predictors for villous atrophy of CD in IDA patients. We used receiver operating characteristic (ROC) curve to evaluate the sensitivity, specificity, and the significant cut off values of ATTGA and ATTGG. Boxplots were used for further evaluation of different factors that affect the Marsh types.

The study considered a  $P < 0.05$  to be statistically significant.

## Results

The prevalence of CD in this cohort was about 10% (222/2238 patients). The GI endoscopic yield for the 499 patients was 72.3% ( $n = 361$ ) with different lesions (Fig. 2), while it was 44.5% ( $n = 222$ ) from those who were referred for CD diagnosis. The mean age of the 499 referred patients was ( $34 \pm 16$ ) years, and it was younger for patients with IDA who were diagnosed with biopsy-proven CD ( $27 \pm 11$ ) years. Also, 86% of patients with CD ( $n = 190$ ) were  $\leq 45$  years old (Table 1). The diagnosis of CD was significantly associated with young age group  $\leq 45$  years, the female gender which encompassed about 90% of patients with CD ( $n = 200$ ), positive celiac antibody screen, and the IDA severity (Tables 1 and 2) using a chi-square test and an ANOVA with a  $P < 0.05$  in the cross-tabulation.

The degree of villous atrophy measured by Marsh classification was significantly related to the degree of IDA severity, presence of GI symptoms at presentation, and the positivity of the celiac serology (Table 2). On further analysis of these significant variables by general univariate analysis, we found that the  $Hb < 9$  g/L and presentation with different GI symptoms had a significant negative correlation with the Marsh type, while the positive ATTGG had a significant positive relationship with the Marsh types (Table 3). We could not make further adjustments of the chosen significant variables by the multinomial logistic regression analysis because the results showed very high statistically unacceptable exp (B) and 95% confidence intervals.

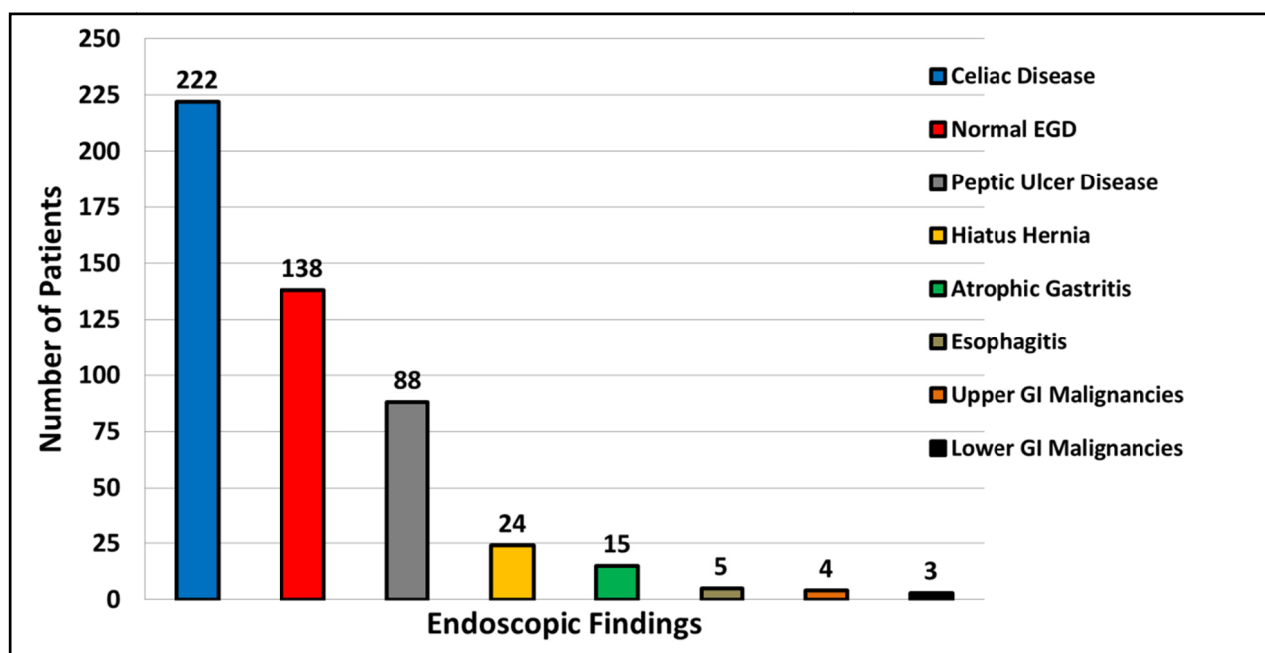


Fig. 2. Bar chart of the different endoscopic findings for the 499 patients with IDA who were referred for a possible celiac disease diagnosis. The endoscopic diagnostic yield for celiac disease is 222/499 patients (44.49%). There were three patients only who underwent lower GI endoscopy with the finding of lower GI malignancies. Abbreviations: EGD, esophagogastroduodenoscopy; GI: gastrointestinal.

**Table 1.** The demographic and general characteristics of 499 patients with IDA who were referred for possible CD diagnosis. The duration of hospitalization was measured for inpatients only

Variable		Biopsy-proven CD n=222 (%)	Negative for CD n=277 (%)	Total n=499 (%)	P-value
Mean age (years) mean ± SD		26.57±10.67	40.62±16.03	34.34±15.55	
Age < 45 years old n (%)		190 (85.59)	125 (45.13)	315 (63.13)	0.001
Female Sex n (%)		200 (90.09)	180 (64.98)	380 (76.15)	0.001
Duration of hospitalization mean ± SD		2.55±1.78	2.59±1.523	2.58±1.582	0.768
Anti-tissue transglutaminase antibody IgA number (%)	Positive Negative Not done	198 (89.2) 12 (5.4) 12 (5.4)	49 (17.69) 102 (36.82) 126 (45.49)	247 (49.50) 114 (22.84) 138 (27.66)	0.001
Anti-tissue transglutaminase antibody IgG number (%)	Positive Negative Not done	155 (69.82) 30 (13.51) 37 (16.67)	40 (14.44) 42 (15.16) 195 (70.40)	195 (39.08) 72 (14.43) 232 (46.49)	0.001
IDA parameters mean ± SD	Mean ferritin µg/L Mean hemoglobin g/L Mean of MCV fL Mean serum iron µg/dL Mean TIBC µg/dL Mean transferrin saturation%	12.52±2.13 9.89±1.77 74.09±9.72 24.50±4.96 384.01±37.82 6.47±1.47	11.03±3.08 8.30±2.48 67.70±12.13 22.43±5.95 418.58±63.43 5.53±1.75	11.69±2.80 9.01±2.33 70.55±11.56 23.35±5.62 403.20±56.22 5.95±1.70	0.001 0.001 0.001 0.001 0.001 0.001

Abbreviations: CD, celiac disease; GI, gastrointestinal; IDA, iron deficiency anemia; Ig, immunoglobulin; MCV, mean cell volume; n, number of cases; SD, standard deviation; TIBC, total iron-binding capacity.

**Table 2.** The relationship between different factors affecting Marsh types in 222 patients with CD and IDA. The percentages (in columns) were approximated to the nearest correct number. All listed factors had significant relationships with the Marsh types (p < 0.005)

Variables	Marsh IIIC n=31 (%)	Marsh IIIB n=172 (%)	Marsh IIIA n=19 (%)
Serum ferritin ≤ 9 µg/L (n=22)	21 (68)	0	1 (5)
Hemoglobin < 9 g/L (n=30)	29 (94)	0	1 (5)
Mean corpuscular volume < 70 fL (n=45)	27 (87)	17 (10)	1 (5)
Serum iron < 15 µg/dL (n=14)	14 (45)	0	0
Total iron binding capacity > 400 µg/dL (n=29)	24 (77)	4 (2)	1 (5)
Transferrin saturation < 3.5% (n=13)	13 (42)	0	0
Availability of GI symptoms (n=172)	23 (77)	140 (81)	9 (47)
Anti-tissue transglutaminase IgA subtype positive (n=198)	20 (65)	165 (96)	13 (68)
Anti-tissue transglutaminase IgG subtype positive (n=155)	5 (16)	138 (80)	12 (63)

Abbreviations: Ig, immunoglobulin; n, number of cases.

**Table 3.** The general univariate analysis model for the significant parameters to the Marsh types in 222 patients with definite celiac disease. Marsh type is the dependent variable. Only the parameters with the significant relationship were mentioned.

Variables	B	SE	p-value	95% C. I.		Observed Power
				Lower	Upper	
Hemoglobin < 9 g/L	-1.009-	0.131	0.001	-1.267-	-0.752-	1.000
Availability of gastrointestinal symptoms	-0.134-	0.051	0.009	-0.235-	-0.034-	0.745
Anti-tissue transglutaminase IgG subtype positive	0.189	0.078	0.016	0.035	0.343	0.672

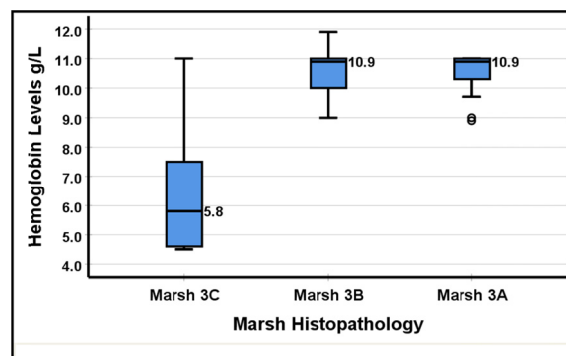
Abbreviations: C.I., Confidence interval; Ig, immunoglobulin; SE, standard error.

Figure 3 illustrates the significant relation between the Hb levels and the Marsh types in patients with CD. The Marsh 3C had the lowest median Hb level in comparison to types 3B and 3A.

ROC curves (Fig. 4) demonstrated the relatively low sensitivity and reasonable specificity of the ATTGA and the ATTGG in evaluating the severity of villous atrophy, with different cutoff values for these antibody subtypes. The ROC curve provided an additional significant relationship of the ATTGA to the Marsh types in suspected patients. This significance was not seen for the ATTGG (Table 4).

There was a stepwise increase in the titers of both ATTGA and ATTGG, which may mirror the severity of the villous atrophy represented by different Marsh types. Patients with Marsh type 3C had the highest titers for both antibody subtypes, while patients with Marsh type 1 had the lowest titers (Fig. 5).

Moreover, 82% of patients with biopsy-proven CD (n = 182) were evaluated as outpatients, and only 40 patients were hospitalized for different durations during the evalu-



**Fig. 3.** Boxplot of Marsh types versus hemoglobin level. The Marsh 3C had the lowest hemoglobin level.

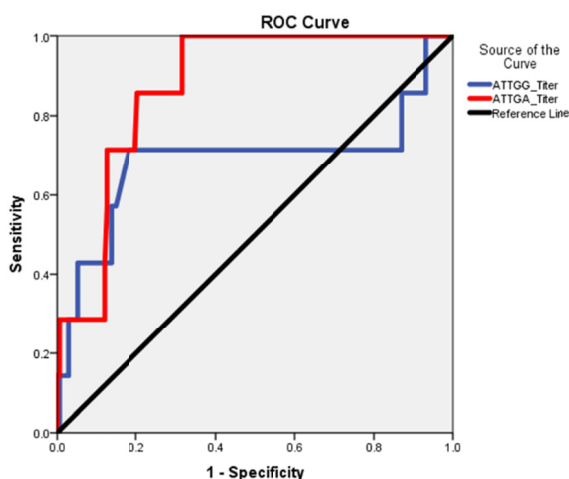


Fig. 4. ROC curve for the anti-tissue transglutaminase antibody subtypes (IgA and IgG). Abbreviations: ATTGA, anti-tissue Transglutaminase IgA subtype; ATTGG, anti-tissue Transglutaminase IgG subtype.

ation process. Still, the length of hospital stay had no significant association with the diagnosis of CD (Fig. 6).

### Discussion

IDA is the most frequent extraintestinal manifestation of CD and may precede the clinical presentation by many years (16). A recent meta-analysis of the studies on CD in IDA described a wide diverse prevalence of CD from 1.8% to 21.3% in patients of Asian and European origin and <9% in those of North American origin (17). The prevalence in Basrah is similar to this international figure. The variation in the local prevalence of CD, enrolment

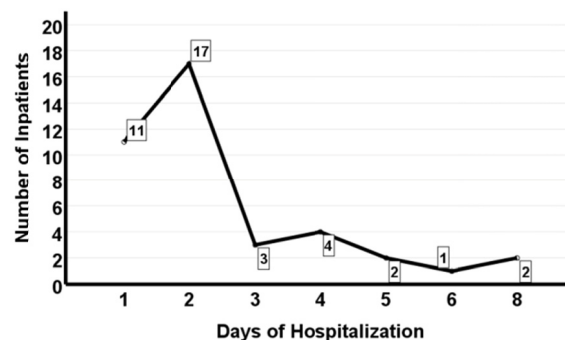


Fig. 6. The days of hospital stay in 40 inpatients referred for diagnosis of CD. There was a non-significant association between the duration of hospital stay and the diagnosis of biopsy-proven celiac disease ( $p=0.535$ ).

criteria, and the availability of different diagnostic procedures for CD with different sensitivity and specificity might be implicated as an explanation for such wide variation in the CD prevalence figures.

The female gender and the young age group were significantly associated with the diagnosis of a biopsy-proven CD of different severity. The age range in this study (18-53 years), the mean age ( $27 \pm 11$  years), and the female preponderance were comparable to previous studies (1,18-21); the higher autoimmune diseases rates in women may mirror that. The guidelines recommend that all premenopausal women with IDA should be screened for CD (10). The CD in this group often goes undetected or under investigated (22).

About 23% of CD patients in this study lack GI symptoms ( $n = 50$ ). Different studies described broad ranges of the prevalence of atypical or silent CD (48%-86%) (1, 2,

Table 4. The findings from the ROC curve for the anti-tissue transglutaminase antibody subtypes (IgA and IgG)

Variable	Cutoff Value U/mL	Sensitivity	Specificity	Area under Curve	p-value	95% C.I.	
						Lower	Upper
ATTGA	17.525	71.4%	80.2%	$0.873 \pm 0.043$	0.001	0.79	0.957
ATTGG	15.95	71.4%	81.9%	$0.688 \pm 0.143$	0.093	0.407	0.968

Abbreviations: ATTGA, anti-tissue Transglutaminase IgA subtype; ATTGG, anti-tissue Transglutaminase IgG subtype; C.I., Confidence Interval.

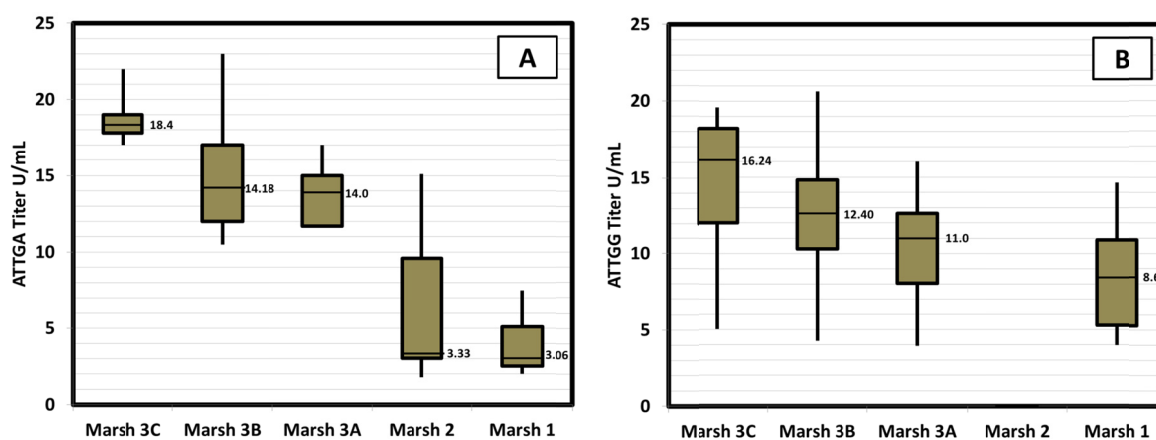


Fig. 5. Boxplots of the different titers of the anti-tissue transglutaminase IgA (panel A) and IgG subtypes (panel B) in different Marsh types in the 499 patients who were referred for diagnosis of CD. The median titers are shown to the right of the corresponding boxplots. The whiskers represent the upper and lower bound of the values range. There were no measurements for the anti-tissue Transglutaminase IgG in Marsh type 2 (panel B). Abbreviations: ATTGA, anti-tissue Transglutaminase IgA subtype; ATTGG, anti-tissue Transglutaminase IgG subtype.

23, 24), and some considered the atypical form as the most common for CD (24).

The old trend in the diagnostic algorithm of CD in IDA depended on site-specific symptoms (25), where the symptomatic patients with malabsorption should be evaluated for CD (6). However, the typical findings are now uncommon (3, 11), and the absence of suggestive symptoms (which are unreliable) causes diagnostic challenges (1, 10) or under-diagnosis of CD (26). The new trend in CD with such protean manifestations is towards a higher proportion of patients presenting with atypical/silent (non-diarrhea) CD, with less severe duodenal fold pathology, indicating a lack of correlation (11, 21, 27). That is why the CD should be considered in any patient with unexplained IDA, even if they lack any GI symptoms (2) or no endoscopic evidence for CD (28, 29).

The celiac serology shows a significant relationship to the definite endoscopic diagnosis of CD, even with their suboptimal sensitivity, specificity (Tables 1-4, Fig. 4). Serological tests are essential in selecting patients for SBBx, even if no apparent cause of IDA can be found, and may negate the need for further testing (3, 10, 11, 30, 31). In high-risk patients, the SBBx should be pursued whatever the celiac serology results (6, 10), even if there was a risk of under-diagnosis of CD (32).

Some authors had criticized the value of gross endoscopic features and SBBx in comparison to the highly sensitive and specific immunological tests. They considered SBBx as an expensive and time-consuming procedure that should be abandoned in favor of celiac serology (11, 33, 34), and restrict them to the high-risk patients, with suggestive endoscopic features (34).

Among our patients who lack the GI symptoms, the degree of villous atrophy is not guided by symptoms, confirming the findings of Brar et al (21), showing that factors other than the degree of duodenal injury must account for their IDA.

The degree of villous atrophy positively correlates ATTGG antibody testing. Two other studies found similar findings concerning ATTGG, not the ATTGA (35, 36). Still, the ROC curves revealed that ATTGA, not the ATTGG, has a significant association with the Marsh types in patients with CD and IDA (Fig. 4, Table 4). These significant relationships between the 2 subtypes of ATTG antibodies and Marsh types can be caused for the stepwise increase of their titers as the severity of villous atrophy increases (Fig. 5).

The presentation of CD in IDA patients had a significant correlation with all the parameters of severe IDA, and the presenting GI symptoms, unlike the findings of many studies (1, 2, 37). On further adjustment, only Hb <9 g/L in symptomatic patients were found to have a strong negative correlation with the severity of villous atrophy; that is, the lower the Hb in symptomatic patients, the higher the degree of villous atrophy (Fig. 3, Table 3), making these variables as strong negative predictors for CD severity, and confirming the results of Zamani et al and Ganji et al (2, 37) but not Brar et al (21).

This study had several limitations. First, several population-specific factors should be considered when evaluating

patients with suspected CD. Second, the observational, cross-sectional nature of the study made us unable to differentiate between the causality and the mere association that may limit the generalizability of the results. Third, the fluctuating accessibility to the serological test may underestimate the real prevalence of CD, especially the scarcity of anti-endomysial antibodies. Fourth, the unavailability of the genetic study for patients who had suspected CD, with no single patient data containing any information about it.

### Conclusion

In conclusion, the 10% prevalence of CD in these 2 centers may be considered as the prevalence in Basrah, because the 2 centers in which the study took place receive most of the cases for the endoscopic evaluation at the study period. The most significant negative predictors for the degree of villous atrophy in individuals with IDA who have a suspicion of CD were the degree of anemia, presence of GI symptoms, and positive celiac serology at different titers.

We need a higher index of clinical suspicion when referring IDA patients for further celiac serology and SBBx to decrease unnecessary investigations, given the atypical or silent forms of CD, and the high percentage of asymptomatic patients at initial presentation.

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### Conflict of Interests

The authors declare that they have no competing interests.

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