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Prevalence of Celiac Disease in Romania

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ABSTRACT

Background & Aims: Celiac disease (CD) is an autoimmune disorder that targets the small intestine, triggered by the ingestion of gluten in genetically predisposed individuals, causing damage to the villi and impairing nutrient absorption. Despite increased awareness and improved diagnostic techniques, CD remains significantly underdiagnosed, with many individuals suffering from unexplained symptoms or misdiagnosed conditions. This study aims to investigate the prevalence and demographic characteristics of CD in a Romanian population using rapid diagnostic tests followed by histological confirmation.

Methods: This cross-sectional study aimed to determine the prevalence of CD in Romania using the BIOHIT Celiac Quick Test among adult participants recruited from tertiary healthcare centers and medical institutions. The prevalence of CD was calculated by dividing the number of confirmed positive cases by the total number of participants, with further evaluation including endoscopy and histological examination for those with positive quick test results. To our knowledge, this is the first prospective study in Romania to assess the prevalence of CD using a serological test.

Results: Out of 713 Romanian participants, 9 tested positive for CD, resulting a prevalence rate of 1.26%. The mean age of the CD-positive group was significantly younger (30.3 years) compared to the general population (49.2 years), and they had a lower mean body mass index (22.2 vs. 28.1). Most CD-positive patients were female (66.7%) and resided in urban areas (55.6%).

Conclusions: Our study found the prevalence of CD in a Romanian population to be slightly higher than the global average, highlighting the effectiveness of rapid diagnostic tests followed by histological confirmation. The significant regional variability in CD prevalence suggests the need for further research into environmental, dietary, and genetic factors, along with enhanced awareness and improved diagnostic protocols to better manage and prevent long-term complications of CD.

Key words: epidemiology – prevalence – celiac disease – digestive symptoms – Celiac Disease Quick Test.

Abbreviations: BMI: body mass index; CD: celiac disease; CDSD: Celiac Disease Symptom Diary; PGI-S: Patient Global Impression of Severity; SD: standard deviation; tTG: tissue transglutaminase; VAS: visual analogue scale.

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder that targets the small intestine. It is triggered by the ingestion of gluten, a protein found in wheat, barley, and rye, in individuals who are genetically predisposed [1]. When these individuals consume gluten, their immune system mounts an inappropriate response that attacks the small intestine [2]. This immune reaction causes damage to the lining of the small intestine, specifically to the villi, which are tiny, finger-like projections responsible for nutrient absorption. As the villi become damaged and flattened, the intestine's ability to absorb nutrients effectively is significantly impaired [3].

The damage to the small intestine caused by CD leads to a wide range of symptoms, which can vary greatly among affected individuals [4]. Gastrointestinal symptoms commonly associated with CD include chronic diarrhea, constipation, abdominal pain, bloating, gas, and unexplained weight loss [3]. Symptomatic CD can present with either gastrointestinal or extraintestinal symptoms due to gluten intake [5]. Classic CD, characterized by malabsorption symptoms like diarrhea

and weight loss, was common before 2000 but now accounts for only 30% of cases. Nonclassical CD, which is the most common presentation today, involves extraintestinal symptoms such as anemia, bone disease, and infertility without the presence of malabsorption. Potential CD describes individuals who have normal intestinal mucosa but positive serology, indicating a higher risk for developing CD [6, 7].

The prevalence of CD in the general population ranges from 0.5% to 2%, with an average of about 1%. This variability in prevalence is influenced by genetic, environmental, and diagnostic factors across different regions [8, 9]. The global seroprevalence of CD, which refers to the presence of antibodies indicating potential CD, is approximately 1.4%. Celiac disease affects all age groups and is more common in females than males, with a prevalence rate of 0.6% in females and 0.4% in males, reflecting a gender ratio of 1.5:1. The prevalence of CD varies significantly by region, with rates of 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania [10, 11]. This gender difference may be attributed to hormonal, genetic, and immunological factors. Additionally, CD is more frequently diagnosed in children than in adults, with a prevalence of 0.9% in children compared to 0.5% in adults [11].

Celiac disease remains significantly underdiagnosed, with many cases still undetected worldwide [12]. Despite increased awareness and improved diagnostic techniques, a substantial number of individuals with CD remain undiagnosed, often suffering from unexplained symptoms or misdiagnosed conditions [10].

Celiac disease affects all age groups, but interestingly, 70% of new diagnoses occur in individuals over 20 years old [13]. This indicates that many adults are being diagnosed later in life. Some of these adults likely had the disease undiagnosed since childhood, experiencing symptoms without a clear cause or diagnosis. In other cases, individuals may develop CD later in adulthood, possibly triggered by environmental factors, infections, or other changes that impact the immune system [14].

Celiac disease exhibits a strong genetic component, as evidenced by epidemiological studies indicating that 7.5–15% of first-degree relatives of affected individuals also have the disease [15]. Concordance rates for CD are notably high among monozygotic twins, ranging from 50–80%, compared to approximately 10% in dizygotic twins. This significant difference underscores the critical role of genetic factors in the disease‘s pathogenesis [16].

The development of CD requires both a genetic predisposition and exposure to dietary gluten [17]. Gluten proteins, primarily gliadins and glutenins, are characterized by a high content of proline and glutamine residues, which render them resistant to complete proteolytic digestion within the gastrointestinal tract. As a result, partially digested gliadin peptides persist and traverse the intestinal epithelial barrier, a process facilitated by increased mucosal permeability commonly observed in individuals with CD [18].

Once these gliadin peptides enter the lamina propria of the intestinal mucosa, they encounter the enzyme tissue transglutaminase (tTG) [19]. This enzyme deamidates the gliadin peptides, converting specific glutamine residues to glutamic acid. This modification significantly enhances the immunogenicity of gliadin, making it more likely to be recognized by the immune system. The deamidated gliadin peptides are then presented by antigen-presenting cells to T cells, leading to the activation of the adaptive immune response [20].

The diagnosis of CD involves serological tests, duodenal biopsies, histological evaluation, and clinical improvement after a gluten-free diet. Genetic testing for HLA susceptibility is increasingly used to assess familial risk [16]. Celiac disease diagnosis requires at least one positive celiac-specific serologic test: anti-tTG, anti-endomysium or anti-gliadin) and histologic changes of modified MARSH grade 2 or higher on small intestinal biopsies. In the absence of serologic data, CD is diagnosed by histologic changes of MARSH grade 2 or higher and clinical or histologic improvement on a gluten-free diet [21]. Histological evaluation, essential for diagnosis and research, assesses gluten-induced injury through quantitative morphometry or grouped classifications, though subjective determination of crypt-villus transition may pose challenges. Celiac disease is a complex multisystem disorder with varied presentations, complicating diagnosis [22]. The 2011 Oslo definitions clarify terminology, with asymptomatic CD referring to patients without symptoms at diagnosis [23].

Over the past two decades, CD has become a significant public health issue [11]. Over the past 50 years, the prevalence of CD has increased significantly, yet many patients remain undiagnosed. This rise in prevalence may be attributed to increased awareness, better diagnostic methods, and changes in environmental factors. Despite these advancements, many individuals with CD continue to live without a diagnosis, leading to ongoing symptoms and potential complications. Improved screening and awareness are essential to identify and treat these undiagnosed cases effectively [24].

The aim of our study is to investigate the prevalence and demographic characteristics of CD within a specific population in Romania, utilizing rapid diagnostic tests followed by histological confirmation to ensure accurate diagnosis. To our knowledge, this is the first prospective study in Romania to assess the prevalence of CD using a serological test.

METHODS

Study Design and Population

This cross-sectional study aimed to determine the prevalence of CD in Romania using quick diagnostic testing kits. The study population consisted of adult participants recruited from tertiary healthcare centers and medical students from various institutions.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were individuals aged 18 years and older, and residents of Romania willing to provide informed consent. Exclusion criteria included individuals with a known diagnosis of CD, those on a strict gluten-free diet, and individuals unable to provide consent.

Quick Testing Kits

We used the BIOHIT Celiac Quick Test. The BIOHIT Celiac Quick Test is a qualitative in vitro immunochromatographic

assay designed to assist in the diagnosis of CD. This test detects antibodies (IgA, IgG, and IgM) against human tissue transglutaminase using whole blood, plasma, or serum samples. It is suitable for use by healthcare professionals in both laboratory-based settings and Point-of-Care (POC) environments. Results can be obtained from a fingertip blood sample within ten minutes.

Procedure

Participants were recruited from tertiary healthcare centers and among medical students. Written informed consent was obtained from all participants.

Data collection included demographic data (age, gender, residence), clinical history (family history of CD, symptoms suggestive of CD), and physical measurements (height, weight) were collected through structured questionnaires administered by trained personnel.

Capillary blood samples were obtained via finger prick from all participants. The BIOHIT Celiac Quick Test was used to analyze the blood samples for the presence of anti-tTG antibodies.

The testing procedure followed the manufacturer's instructions. Test results were read within ten minutes and recorded as either positive, negative, or indeterminate.

Confirmation of Positive Results

All participants with positive quick test results underwent further evaluation with endoscopy and histological examination to confirm the diagnosis of CD. Histological confirmation was based on the presence of characteristic changes in the small intestine, classified according to the Marsh criteria.

Questionnaires and Symptom Assessment

For participants confirmed to have CD, we administered several questionnaires to assess their quality of life and symptom severity. These included the Celiac Disease Symptom Diary (CDSD), the EQ-5D-5L Visual Analogue Scale (VAS), and the Patient Global Impression of Severity (PGI-S) scale. Additionally, participants were asked to report the presence of symptoms experienced in the last six months, providing a comprehensive overview of their symptomatology.

Data Analysis

Data were analyzed using descriptive statistics to determine the prevalence of CD. The prevalence rate was calculated by dividing the number of confirmed positive cases by the total number of participants, expressed as a percentage. Confidence intervals (95%) were calculated to provide an estimate of the precision of the prevalence rate.

RESULTS

Description of the General Population

A total of 713 individuals participated in the study, undergoing initial screening with a rapid diagnostic test for CD. The mean [±standard deviation (SD)] age of the participants was 49.2 (±16.3) years. The age distribution of the participants was as follows: 19.8% were under 40 years of age, 44.7% were between 40 and 64 years, and 35.5% were 65 years or older.

The gender distribution showed a higher proportion of females (58.9%) compared to males (41.1%). In terms of residence, a majority of the participants were from urban areas (63.0%), while the remaining 37.0% resided in rural areas.

The mean (±SD) body mass index (BMI) of the participants was 28.1 (±3.8). The height of the participants averaged 170.5 cm (±12.5), and the average weight was 82.2 kg (±16.5).

Prevalence of Celiac Disease

Out of the 713 individuals tested with the rapid diagnostic test, 9 tested positive for celiac disease. Following the initial positive result from the rapid test, these 9 individuals underwent histological examination to confirm the diagnosis. All 9 positive cases from the rapid diagnostic test were confirmed histologically, confirming the presence of CD. This results in a prevalence rate of approximately 1.26% within the sampled population.

Description of the Celiac Disease Population

The CD population consisted of 9 individuals, confirmed histologically after initial positive results from the rapid diagnostic test. The mean (SD) age of the CD patients was 30.3 (4.0) years. Most of the CD patients were under 40 years of age, indicating a younger demographic compared to the general population.

The mean (SD) BMI of the CD patients was 22.2 (1.8), which is lower than that of the general population. The height of the CD patients averaged 169.7 cm (11.1), and the average weight was 64.4 kg (9.9).

In terms of gender, 66.7% of the CD patients were female, and 33.3% were male. The residence distribution showed that 55.6% of the CD patients lived in urban areas, while 44.4% resided in rural areas (Table I).

Table I. Demographics and clinical characteristics of study participants

Characteristic	All Participants (N=713)	CD positive (N=9)	CD negative (N=704)
Age (years), mean±SD	49.20 ± 16.29	30.33 ± 3.97	49.44 ± 16.24
BMI, mean±SD	28.15 ± 3.83	22.23 ± 1.84	28.22 ± 3.79
Height (cm), mean±SD	170.46 ± 12.47	169.67 ± 11.11	170.47 ± 12.50
Weight (kg), mean±SD	82.23 ± 16.48	64.44 ± 9.94	82.45 ± 16.42
Gender (female), %	58.91	66.67	58.67
Residence (urban), %	62.97	55.56	63.07

SD: standard deviation; BMI: body mass index

Symptomatology in CD Patients

The CD population exhibited a range of gastrointestinal and nonspecific symptoms. The most reported symptoms included bloating and flatulence, each affecting a significant portion of the CD patients. Constipation and diarrhea were also frequently reported, along with nausea. Other symptoms such as abdominal pain, heartburn, indigestion, vomiting, and weight loss were present but less common among the CD patients. These symptoms reflect the typical clinical presentation of CD, emphasizing the importance of early diagnosis and management to alleviate these symptoms and improve patient quality of life (Fig. 1).

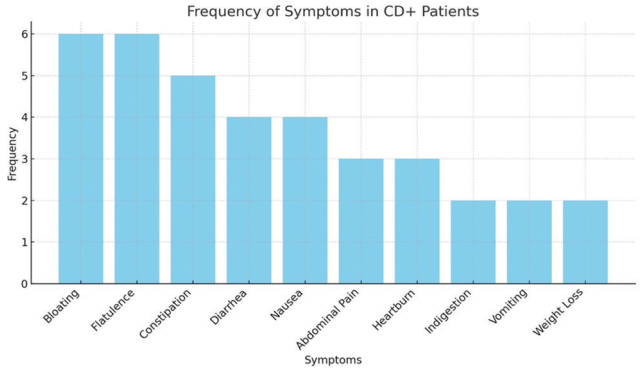

Fig. 1. Frequency of symptoms in CD patients.

Quality of Life Assessments

We administered several questionnaires to assess the quality of life and symptom severity in patients with CD. The results are summarized in Table II.

Table II. Questionnaire Scores in CD Patients

Questionnaire	Mean Score	Standard Deviation
CDSD	3.44	1.13
EQ-5D-5L - VAS	62.22	17.02
PGI-S Scale	3.44	1.33

CDSD: Celiac Disease Symptom Diary, EQ-5D-5L – VAS: EuroQol Five Dimensions Five Levels Visual Analogue Scale, PGI-S: Patient Global Impression of Severity scale.

The quality-of-life assessments indicated that patients CD experience moderate symptom severity and health status impact. The scores from the CDSD reflected a moderate level of symptom severity. Similarly, the EQ-5D-5L VAS scores suggested a moderate overall health status. The PGI-S scale scores also indicated moderate severity.

Age Comparison

A t-test was conducted to compare the age of the CD and non-CD groups. The test results revealed a t-statistic of -3.52 and a p-value of 0.00045. These findings indicate a statistically significant difference in age between the two groups, with the CD group being significantly younger than the non-CD group. This suggests that CD may be more prevalent or more readily diagnosed in younger individuals.

BMI Comparison

A t-test was also performed to compare the BMI of the CD and non-CD groups. The analysis yielded a t-statistic of -4.68 and a p-value of 0.000004. These results indicate a statistically significant difference in BMI between the CD and non-CD groups, with the CD group having a significantly lower BMI.

Gender Comparison

To examine the gender distribution between the CD and non-CD populations, a chi-squared test was conducted. The chi-squared test results showed a chi2-statistic of 0.018 and a p-value of 0.892, indicating no statistically significant difference in the sex distribution between the two groups. This suggests that CD affects males and females equally in this sample.

DISCUSSION

The use of the rapid diagnostic test proved effective as an initial screening tool, enabling the identification of potential CD cases quickly and efficiently. The subsequent histological confirmation provided a reliable method to ensure the accuracy of the CD diagnosis [25]. This two-step diagnostic approach not only streamlines the identification process but also ensures high diagnostic accuracy, minimizing the chances of false-positive results.

The prevalence of CD in our study population was found to be approximately 1.26%, based on the results of rapid diagnostic tests followed by histological confirmation. To our knowledge, this is the first prospective study in Romania to assess the prevalence of CD using a serological test. This prevalence rate is consistent with various regional and global estimates but exhibits some notable differences when compared with data from other studies and regions [11]. Our prevalence rate of 1.26% aligns closely with several reported prevalence rates but is notably higher than the global prevalence of 0.77% estimated in a 2021 comprehensive analysis. This global estimate, derived from multiple studies worldwide, highlights that nearly 1 in 130 people are affected by this autoimmune disorder. Such data emphasize the significance of CD as a global health concern, necessitating continued awareness and diagnostic efforts. For comparison, Hungary reports a prevalence rate of 1.38%, Italy 1.24%, and Germany between 0.8% and 1.12% [26, 27]. The higher prevalence in our study could be attributed to regional dietary patterns, genetic predispositions, or methodological differences in data collection.

In Eastern Europe, little is known about the prevalence of CD. A previous study conducted in Romania, which took place in 2002, reported a higher prevalence rate of 2.22% among adults biopsied during upper endoscopy. It should be noted that this study included patients from endoscopic centers, which typically see higher numbers of individuals requiring investigation, potentially influencing the prevalence rate observed [28].

Significant regional variability in CD prevalence has been observed. For instance, in Asia, the prevalence ranges from 0.69% overall, with Saudi Arabia reporting the highest rate at 1.42% and Japan the lowest at 0.05%. This variability indicates that environmental, dietary, and genetic factors significantly

influence the prevalence of CD. In particular, the higher rates in Saudi Arabia may be linked to dietary habits, including high wheat consumption, which increases gluten exposure, a known trigger for CD in genetically susceptible individuals [26].

In Iran, a 2017 systematic review and meta-analysis reported CD prevalence rates of 3% using serological tests and 2% using biopsies. These findings illustrate a notable difference between the rates identified through blood tests and tissue biopsies, emphasizing the need for accurate diagnostic methods to avoid over- or under-diagnosis [29].

The prevalence of CD in Europe, based on studies using serological tests, ranged from 1.4% to 24.5%, while studies using intestinal biopsy reported a prevalence of 1.1% to 16.6%. This variation can be attributed to differences in diagnostic methods, geographic location, and environmental and genetic factors. The high variability in prevalence rates underscores the necessity of standardized diagnostic criteria and increased awareness to ensure accurate diagnosis and appropriate management of CD [30, 31].

Celiac disease is highly prevalent in Europe, yet remains notably underdiagnosed across all countries, even in countries with high awareness like Finland. A study by Mustalahti et al. [32] found that the ratio of diagnosed cases to total prevalence varied from 6% in Italy to 24% in Finland. Despite the widespread prevalence, many individuals with CD go undetected, leading to potential long-term health complications. This widespread underdiagnosis underscores the necessity for improved screening and diagnostic practices to effectively identify and manage the disease [32]. Enhanced public awareness and education regarding CD symptoms and risks are essential to address this significant health challenge. Our study emphasizes the importance of understanding CD prevalence and distribution to identify at-risk populations and refine diagnostic strategies and healthcare planning. The underdiagnosis in both children and adults necessitates increased awareness among healthcare providers and general population about the diverse presentations of CD. Early detection and treatment are critical to prevent long-term health complications and improve quality of life. The rising prevalence of CD highlights the urgent need for enhanced screening methods and greater emphasis on recognizing non-classical symptoms. Public health initiatives and medical research are increasingly focusing on early detection, patient education, and the development of effective treatment protocols to mitigate the impact of this autoimmune disorder triggered by gluten consumption [33, 34].

High CD rates in different areas may be due to eating habits and high wheat consumption, increasing gluten exposure [35]. This suggests that dietary patterns, particularly the consumption of gluten-rich foods like wheat, play a significant role in the higher prevalence of CD in this region, as gluten is a known trigger for the disease in genetically susceptible individuals [29].

Celiac disease exhibits a higher incidence among females and the younger population, with a notable rise in cases from the latter half of the 20th century into the 21st century in the Western world [36]. Although the global incidence of CD requires further elucidation through population-based studies in Africa, Asia, and Latin America, current trends highlight significant demographic patterns. Our study indicates the younger age of the CD population, potentially attributable to enhanced screening practices, heightened awareness of symptoms, or intrinsic age-related prevalence differences, warranting further investigation [37]. Contrary to some literature suggesting a female predominance in CD diagnosis due to increased health-seeking behavior or differential symptomatology, our data did not demonstrate significant gender-based disparities. Furthermore, an upward shift in the median age of adult diagnosis post-1985, from 34 to between 44 and 46 years, underscores a delayed diagnosis trend in more recent years [34, 38].

Our study found a statistically significant difference in BMI between the CD and non-CD groups, with the CD group having a significantly lower BMI. This finding is consistent with the known pathophysiology of CD, which often involves malabsorption and nutritional deficiencies leading to lower body weight and BMI. The significantly lower BMI in the CD population underscores the importance of nutritional management and monitoring in individuals with CD to prevent complications related to malnutrition. However, it is important to note that CD is not always associated with malnutrition and weight loss. Literature indicates that about half of the patients with CD have a normal BMI, one-third are underweight, and one-fifth are overweight. This variation suggests that individuals with CD can also have normal weight or be overweight, reflecting the diverse clinical presentations of the disease [34]. Therefore, while lower BMI is a significant concern in many CD patients, healthcare providers should also be aware of the potential for normal or increased BMI in this population, ensuring a comprehensive approach to diagnosis and management.

The study data indicated that abdominal pain, bloating, and constipation are the most prevalent gastrointestinal symptoms in CD patients, aligning with findings from a 2021 study in Hamedan, Iran, and a 2011 U.S. study, both of which identified abdominal pain and diarrhea as the most common symptoms in CD patients. Our study further supports these findings, showing that the CD population experiences a range of gastrointestinal and nonspecific symptoms, with bloating and flatulence being particularly common. Constipation and diarrhea were also frequently reported, along with nausea. Additionally, other symptoms such as abdominal pain, heartburn, indigestion, vomiting, and weight loss were observed, albeit less commonly. These symptoms highlight the typical clinical presentation of CD, underscoring the necessity for early diagnosis and management to mitigate these symptoms and enhance patient quality of life. The varied symptomatology reflects the complex nature of CD and emphasizes the importance of comprehensive clinical evaluation to ensure timely and effective intervention [34].

The findings from our study, along with comparisons to global and regional data, highlight the critical need for enhanced diagnostic protocols and increased awareness of CD. In regions with high CD prevalence, it is imperative to investigate dietary patterns, especially high gluten consumption, to understand their impact on the development of CD. Healthcare professionals must be trained to recognize the diverse presentations of CD to improve diagnosis rates.

Understanding the prevalence and distribution of CD is essential for identifying at-risk populations, refining diagnostic strategies, and optimizing healthcare planning to better manage and support those affected by this autoimmune disorder. The significant underdiagnosis in both children and adults underscores the necessity for heightened awareness among healthcare providers and the general public about CD's varied symptoms. Early detection and treatment are crucial to prevent long-term health complications and improve the quality of life for those with CD. Enhanced screening methods and a focus on recognizing non-classical symptoms can facilitate the identification and diagnosis of more CD cases, ensuring timely intervention and management. The rising prevalence of CD has emphasized the need for increased awareness and improved diagnostic strategies. As an autoimmune disorder triggered by gluten consumption, CD can lead to severe health complications if left untreated. Consequently, public health initiatives and medical research have increasingly focused on early detection, patient education, and the development of effective treatment protocols to manage and mitigate CD's impact on affected individuals.

Our study presents several strengths and limitations in the context of diagnosing and understanding the prevalence of CD. One key strength is the use of the rapid diagnostic test as an initial screening tool, followed by histological confirmation, which ensures high diagnostic accuracy and minimizes false-positive results. This two-step diagnostic approach streamlines the identification process, making it both efficient and reliable. Additionally, the study's inclusion of a population predominantly from a part of Romania provides valuable regional insights.

However, the study also has notable limitations. The significant regional variability in CD prevalence suggests that environmental, dietary, and genetic factors play crucial roles, necessitating further investigation into high gluten consumption areas to understand their impact on CD development. The underdiagnosis of CD, particularly in regions like Europe, highlights the need for improved screening methods and increased awareness among healthcare providers and the general population. Moreover, the study's focus on a specific regional population may limit the generalizability of the findings to other populations with different dietary patterns and genetic backgrounds.

Overall, while the study contributes valuable insights into CD diagnostic strategies, it underscores the ongoing need for enhanced diagnostic protocols, public health initiatives, and medical research to address the challenges associated with this autoimmune disorder.

CONCLUSIONS

Our study highlights the prevalence of CD in a Romanian population as slightly higher than the global average but consistent with regional trends. The utilization of rapid diagnostic tests followed by histological confirmation proved to be an effective and reliable approach, ensuring high diagnostic accuracy. The study's strengths include its comprehensive diagnostic process and the inclusion of a diverse demographic, providing valuable insights into the regional prevalence and presentation of CD. However, the significant regional variability in CD prevalence suggests the need for further investigation into environmental, dietary, and genetic factors that may influence disease development.

The discrepancies between serological and biopsy-confirmed diagnoses underscore the necessity for accurate and standardized diagnostic approaches. Enhanced awareness, improved diagnostic protocols, and further research are crucial to address the burden of CD effectively. Increased awareness among healthcare providers and the general population about the diverse presentations of CD, coupled with early detection and management, is essential to prevent long-term health complications and improve the quality of life for those affected by this autoimmune disorder.

Conflicts of interest: None to declare.

Authors' contribution: A.P., S.L.P and D.L.D. conceived and designed the study. A.P., D.D.P., A.I. and S.G. contributed to the acquisition, analysis and interpretation of data. A.P. and S.L.P drafted the manuscript. S.L.P and D.L.D. critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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