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Original Article

Latent class analysis identifies novel coeliac disease subgroups with distinctive clinical features: a multicentric study

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ABSTRACT

Background: Coeliac disease (CD) is a lifelong, immune-mediated disorder characterised by a wide clinical spectrum, which often challenges traditional classifications like the Oslo definitions. We aimed to recognise novel CD subtypes based on clinical features using latent class analysis (LCA) and validate these phenotypes with a predictive supervised model.

Methods: In this multicentric retrospective study, 2478 adult CD patients from 19 Italian centres (2011–2021) were analysed. Clinical, laboratory, endoscopic, and histological data were collected. LCA was applied to categorical symptom variables, including gastrointestinal, haematological, neuropsychiatric manifestations, and fatigue, to identify latent clusters, with the optimal number of classes determined by the Bayesian Information Criterion. The newly derived classes were compared with the traditional Oslo classification using Chi-squared tests, while multinomial logistic regression (MLR) was employed to validate the associations between latent classes and additional features.

Results: LCA identified four classes, namely Class 1 (predominant lower gastrointestinal symptoms); Class 2 (upper gastrointestinal manifestations); Class 3 (mainly asymptomatic or nonspecific cases); and Class 4 (microcytic anaemia with asthenia). Comparison with the Oslo classification revealed partial overlap, indicating potential misclassification under current criteria. MLR confirmed significant associations, with female sex strongly linked to Class 2 (OR 2.7, 95 % CI 1.52–4.78). Autoimmune comorbidities (OR 1.96, 95 % CI 1.18–3.25) and severe histological damage (B2 Corazza-Villanacci classification, OR 9.12, 95 % CI 1.86–44.63) were also more frequent in Class 2.

Conclusions: LCA may offer a novel, data-driven approach to refine CD phenotyping that should be validated in future studies.

1. Introduction

Coeliac disease (CD) is a chronic, lifelong, immune-mediated disorder causing villous atrophy in genetically susceptible individuals upon the ingestion of gluten in the diet [1,2]. It has been recently reported that the global pooled seroprevalence and prevalence of biopsy-confirmed CD are 1.4 % and 0.7 %, respectively, though with some geographical differences, and the incidence has markedly increased over the last three decades [3]. Nonetheless, some studies suggest that a notable proportion of patients remain undiagnosed, [4] due to the lack of symptoms, poor case-finding strategies, or because subtle or mild symptoms can escape medical attention.

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Notably, the proteiform and heterogeneous clinical spectrum of CD has been largely described in several series, and includes asymptomatic cases, intestinal (e.g., diarrhoea or constipation, abdominal pain, flatulence, dyspepsia) and extra-intestinal manifestations (e.g., neurological alterations, fatigue, anaemia and other haematological abnormalities), and a strong association with several other autoimmune disorders (e.g., autoimmune thyroid disease, vitiligo) [1,2,5]. An attempt to categorise the clinical presentation of CD is represented by the Oslo classification, a seminal consensus of experts who proposed the use of the definitions asymptomatic CD (i.e., CD not accompanied by symptoms even in response to direct questioning at initial diagnosis), classical CD (i.e., CD presenting with signs and symptoms of malabsorption, such as diarrhoea, steatorrhea, weight loss, anaemia, growth failure), non-classical CD (i.e., CD presenting without signs and symptoms of malabsorption), and subclinical CD (i.e., CD that is below the threshold of clinical detection) [6].

Although this clinical classification has been used for years -and it is still in use- its validity in fully depicting CD phenotypes, or in capturing the risk of developing complications, is uncertain. Some studies suggest that patients with classical CD are more prone to the development of complications with respect to patients with subclinical or asymptomatic CD [7]. However, it is unclear whether specific CD subgroups are more likely to exhibit other peculiar features. In this regard, artificial intelligence (AI) has recently gained significant attention in gastroenterology, particularly in endoscopy, where diagnostic imaging represents one of the most promising fields for AI applications [8,9]. Indeed, classifying CD based on clinical and other features using AI may provide novel and important insights for its management, as has been the case for irritable bowel syndrome (IBS). In a recent study, [10] the authors applied latent class analysis (LCA) and identified seven distinct IBS clusters, categorised according to clinical features and psychological burden, which are useful for tailoring *ad hoc* interventions [11]. Such an attempt to cluster CD phenotypes using LCA has never been made.

Building on these premises, we explored the possibility of identifying CD subtypes based on clinical features using data from a multicentric cohort of CD patients through LCA and examined whether these subtypes could be supported by a predictive supervised model.

2. Methods

2.1. Description of the dataset

This was a multicentric, retrospective, study which examined numerous clinical, laboratory, endoscopic, and histological variables analysed in a sample of adult CD patients evaluated at 19 Italian centres between 2011 and 2021. Centres are spread from north to south of Italy, reflecting a wide range of geographical areas throughout the country. This paper is a sub-analysis of a cohort of patients already described in another study focusing on the diagnostic delay of CD, and where we collected several sociodemographic and clinical data [12]. According to the available guideline, the diagnosis of adult CD [13,14] was based on both a positive CD serology (anti-tissue transglutaminase IgA and/or anti-endomysial antibodies IgA; IgG were considered in case of IgA deficiency) and a duodenal biopsy showing any degree of villous atrophy. All patients were classified into three classes, namely classical, non-classical, and asymptomatic. Patients with potential CD, refractory CD, or enteropathy-associated T-cell lymphoma were excluded due to the small sample size. For the purposes of the present study, among all data collected, we included sociodemographic variables (sex, age at diagnosis), and clinical variables, such as symptoms, manifestations or other relevant data at onset (gastrointestinal and extra-intestinal including fatigue, anaemia, infertility, dermatitis herpetiformis, osteoporosis, family history of CD), Corazza-Villanacci or Marsh-Oberhuber classifications, CD antibody status, and autoimmune comorbidities (e.g., Sjogren syndrome, type 1 diabetes mellitus, autoimmune thyroid disease, vitiligo). All reported symptoms, comorbidities, and clinical features pertain to the time of CD diagnosis. Other variables, such as smoking status, ethnicity, years of education, marital status, as well as the details of the inclusion/exclusion criteria and the full list of symptoms or conditions that were present at the time of diagnosis and that prompted further work up for establishing the diagnosis of CD have already been reported in a previous paper [12]. For the purpose of the analysis, we eventually used the Corazza-Villanacci classification since this was the most widely available across the enrolling centres. Finally, under the variable misdiagnosis we collected all the wrong diagnoses that were made before CD was correctly identified. All patients provided written informed consent before entering the study, and the protocol was approved by the local Ethics Committee (2014). The STROBE guidelines were followed for quality assurance. The data supporting our findings cannot be shared publicly but are available upon motivated request addressed to the corresponding author. No patients or members of the public were involved into the design or interpretation of the study.

2.2. General workflow

Fig. 1 shows the general workflow of the study. Unsupervised and supervised methods were combined to find and validate the possible classes. The first step was the application of an unsupervised method on a selected set of symptoms, including gastrointestinal (GI) symptoms (i.e., dyspepsia, gastroesophageal reflux disease, vomit, diarrhoea, meteorism, abdominal pain, anorexia, and weight loss), haematological abnormalities (i.e., microcytic, macrocytic or normocytic anaemia, thrombocytopenia, and pancytopenia), neuropsychiatric abnormalities (i.e., paraesthesia, psychiatric disorders, others), and fatigue.

Considering that all the variables could be categorised, we used LCA, a probabilistic unsupervised approach (see later) [15]. After the identification of the latent classes, we used a multinomial logistic regression (MLR) on the remaining variables (i.e., histological, serological, genetic, and clinical complications), excluding the symptom variables used for LCA. This approach has the advantage of both validating the new classes verifying whether they have an association with the remaining variables and characterizing how the different variables are associated the most with the classes thanks to the calculation of the odds ratios (OR).

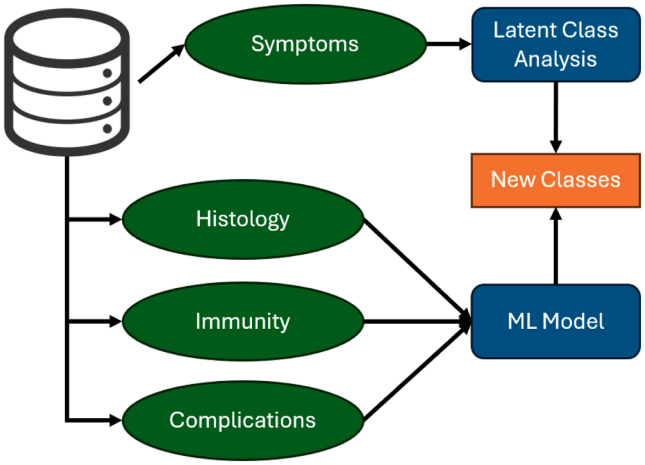

Fig. 1. General workflow of the study. Symptoms at diagnosis of coeliac disease (CD) were used for identifying the novel Classes through the latent class analysis (LCA). Subsequently, the LCA-identified classes were compared with the traditional Oslo classification, and multinomial logistic regression (MLR) was employed to validate the associations between latent classes and additional features, such as histological damage, association with other autoimmune disorders, and complications. By complications, we do not mean complicated CD (i.e., refractoriness, enteropathy-associated T-cell lymphoma), but rather those complications related to malabsorption (e.g., osteoporosis, infertility).

2.3. Latent class analysis

As mentioned, LCA is a probabilistic method used to find groups or subclasses in multivariate categorical data [15]. It relies on the idea that the data can be described by a mixture of latent distributions [16]. Despite the term *class* in its name, LCA is an unsupervised approach, as the observations are not labelled in specific classes, but are supposed to be groupable in latent classes (clusters) that are unknown at the beginning of the procedure. Like most unsupervised methods, the number and type of clusters is not unique, as the data can be defined in different ways depending on the clusters' characteristics. In LCA, however, there are several procedures that can be used to assess the fitness of the model and determine the best number of classes, for example through use of the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC). In this paper, we implemented LCA on the data using the R package "poLCA", using BIC to select the best number of latent classes. The differences between the Oslo classification and the novel latent class categories were compared with Chi-squared test. For all significant results, a pairwise Chi-squared test has been performed on each pair of variables with the correction of Bonferroni to identify significantly different subclasses. A p-value <0.05 was considered as statistically significant.

2.4. Class validation through multinomial logistic regression

MLR is a supervised machine learning method used for classification of multiclass problems, i.e. problems involving datasets that contain more than two classes. It can be considered an extension of standard logistic regression, that performs binary classification through the estimation of the parameters of a logistic function. This approach offers several advantages, one of which is the possibility to easily inspect the effect of the individual features on the outcome through the calculation of OR. In our study, we used it to explore the relation that the LCA classes have with the variables that have not been used to create the classification, i.e., the features regarding histology, serology, and HLA. Sex and complications have been included as well to account for their confounding effects.

3. Results

A total of 2478 adult patients (1872 female, 75.5 %, median age at diagnosis 38 years, IQR 27–46) were included in the final dataset, from a larger cohort of 3546 individuals. Some patients were excluded because they did not meet the inclusion criteria or some data important for the study were not available. Only for a minority of variables some data were missing as follows: weight (15.7 %), height (18.0 %), presence of associated autoimmune disorders (0.2 %), anti-tissue transglutaminase antibodies (9.1 %), and the Corazza-Villanacci histological grading (4.2 %). Among the included patients, 1314 (53.0 %; 77.0 % female, median age 39 years) were categorised as classical CD, 876 (35.4 %; 77.5 % female, median age 38 years) were categorised as non-classical CD, and 288 (11.6 %; 62.8 % female, median age 38 years) were categorised as asymptomatic CD.

3.1. Latent classes

In order to find the proper number of latent classes that allows to have a balance between performance and overfitting, we run the LCA model described in the methods section nine times, setting a range of number of classes between two and ten, and evaluating the BIC. With this procedure, LCA selects four as the best number of classes. Fig. 2 shows a heatmap of the probability of each symptom to be found in each latent class, highlighting the main characteristics of the clusters found by the model. Several characteristics of the new classes can be noticed from this figure, including Class 1 (291 patients; 74.9 % female, median age 38 years), encompassing patients who show mainly symptoms of the lower GI tract such as diarrhoea, abdominal pain, and meteorism, while they usually do not complain of upper GI symptoms; Class 2 (144 patients; 76.4 % female, median age 40 years), encompassing patients with upper GI manifestations such as dyspepsia (present in all patients) and gastroesophageal reflux disease; Class 3 (1278 patients; 67.7 % female, median age 38 years), encompassing asymptomatic patients or patients without a prominent feature; Class 4 (765 patients; 88.6 % female, median age 38 years), encompassing patients with microcytic anaemia, often with coexisting asthenia, occasionally showing other concurrent symptoms. Class 3 is the largest one, showing that most patients do not have specific symptoms. Class 4 is the second in terms of patient number and is mostly composed by female patients.

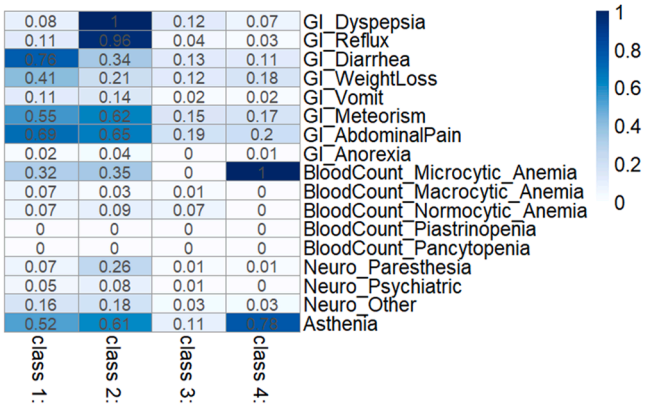

Fig. 2. Heatmap of the probability of each symptom to be found in each one of the latent classes. Four distinctive classes were identified, underlying different clinical phenotypes.

The matching between the Oslo classification and the latent classes found by our model is shown in a Sankey diagram in Fig. 3. As expected, most individuals in Class 1 (lower GI symptoms) were classified as classical CD in the Oslo classification, and most asymptomatic patients fall in Class 3 in the LCA classification. However, several patients in Classes 3 and 4, who most likely do not have any GI symptoms, are currently classified as classical CD, denoting some possible uncertainty in the way they have been classified by the clinicians.

3.2. Differences between the Oslo and the latent class classifications

After defining the new classes with LCA, we evaluated the proportion of patients with specific characteristics or complications in both

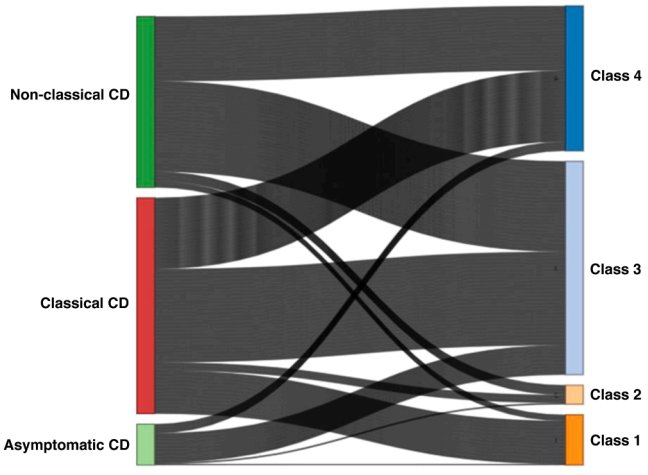

Fig. 3. Sankey diagram showing the correspondences between the Oslo classification (left-hand side) and the novel classes (right-hand side).

classifications to perform a preliminary investigation on the possible relations between the selected symptoms and the clinical outcomes. We evaluated previous misdiagnosis, family history of CD, infertility (only in females), osteoporosis, dermatitis herpetiformis, and associated autoimmune disorders.

Table 1 reports the proportions of patients categorised according to both classifications for all these variables, except for previous misdiagnosis and associated autoimmune disorders (which will be reported later). In the novel LCA classification, no differences were found regarding family history across the four Classes, while significant differences were found for infertility (significantly more common in Class 2), osteoporosis (significantly more common in Classes 1 and 4), and dermatitis herpetiformis (significantly more common in Class 3). Supplementary Figure 1 reports the distribution of the variables family history, infertility, osteoporosis, and dermatitis herpetiformis according to the Oslo classification VS the novel LCA classification.

Supplementary Table 1 shows the proportion of patients who were misdiagnosed according to the Oslo definitions and the new LCA classification. Looking at the results on the new classes, patients in Class 3, that include most asymptomatic patients, have the lowest proportion of previous misdiagnosis, while Class 2 patients, mostly with upper GI tract symptoms, where the most misdiagnosed.

Supplementary Table 2 reports the differences of patients with at least one autoimmune condition or multiple autoimmune comorbidities according to the Oslo vs the LCA classes. A significant difference was noticed in the asymptomatic class, having a higher proportion of autoimmune comorbidities. Regarding multiple autoimmune comorbidities, Class 2 patients, characterised by upper GI symptoms, were significantly more affected than Class 4.

3.3. Binarization based on sex

As shown in Fig. 4, LCA extracted four Classes with the same characteristics of the general model for females, and three Classes for males, with the same characteristics of Classes 1–3 of the general model. Of note, Classes 1 and 2 are better defined in the male model, as almost nobody in Class 1 had upper GI symptoms, whereas all patients in Class 2 had gastroesophageal reflux disease. Since there was no Class 4 for males, patients with anemia were distributed in Classes 1–3, most of them being in Class 1

3.4. Multinomial logistic regression

Table 2 shows the OR, the p-value, and the 95 % confidence interval of the two MLR models created with both the LCA and the Oslo classes. The LCA OR are referred to the probability of belonging to Classes 2, 3 and 4 with respect to Class 1, whereas the OR of the Oslo classification had the asymptomatic class as reference. Concerning the LCA classes, female sex is associated with a higher probability of being in Class 2 (OR 2.7), as are the presence of autoimmune diseases (OR 1.96), a normal aspect of duodenum (OR 8.11), and a B2 Corazza-Villanacci histology (OR 9.12). For the Oslo classification, the presence of any complications (OR 4.61) and infertility (OR 2.65) were more common in the non-classical group.

4. Discussion

This study is an initial attempt to explore the use of LCA in refining the phenotypic classification of CD and may provide a basis for considering alternatives to the traditional Oslo classification [6]. By applying LCA to a large multicentric cohort of 2478 adult CD patients from 19 Italian centers, our study highlights the clinical heterogeneity of CD and suggests four novel latent Classes which are based on clinical features. However, these results should be interpreted with caution in the light of this setting, and warrant confirmation in independent cohorts and future studies.

Table 1
Proportions of patients with specific clinical features, along with p-values and the pairwise tests with Bonferroni correction.

	Oslo classification				New classes			
		No	Yes	P-Value		No	Yes	P-Value
Family history	Classical	1070	244	<0.001	Class 1	238	53	0.015 *(>0.05 in pairwise comparisons with Bonferroni correction)*
	Non-classical	717	159		Class 2	116	28	
	Asymptomatic	142	146		Class 3	962	316	
	–	–	–		Class 4	613	152	
Infertility	Classical	877	135	0.014 *(0.017 pairwise comparison classical* vs *non-classical)*	Class 1	182	36	0.001 *(0.0017 pairwise comparison Classes 2* vs *3)*
	Non-classical	554	125		Class 2	81	29	
	Asymptomatic	149	32		Class 3	754	112	
	–				Class 4	563	115	
Osteoporosis	Classical	1076	238	0.067	Class 1	231	60	<0.001 *(0.01 Classes 1* vs *3, <0.001 Classes 4* vs *3)*
	Non-classical	743	133		Class 2	122	22	
	Asymptomatic	249	39		Class 3	1109	169	
	–				Class 4	606	159	
Dermatitis herpetiformis	Classical	1289	25	<0.001 *(0.02 non-classical, 0.0024 classical* vs *asymptomatic)*	Class 1	283	8	<0.001 *(0.0009 pairwise comparison Classes 3* vs *4)*
	Non-classical	841	35		Class 2	140	4	
	Asymptomatic	272	16		Class 3	1223	55	
	–				Class 4	756	9	

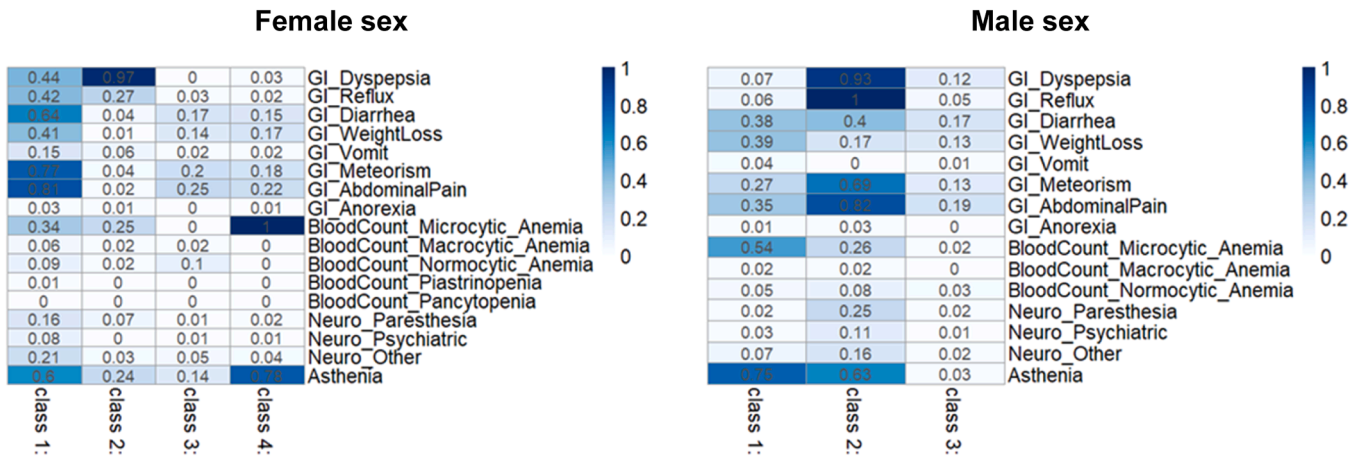

Fig. 4. Heatmap of the probability of each symptom to be found in each one of the latent classes in either females (left-hand side) or males (right-hand side).

Table 2
Odds ratios (with 95 % confidence intervals) of the multinomial logistic regression coefficients with the LCA VS the Oslo classes.

	LCA Classification			Oslo Classification	
Variable	Class 2	Class 3	Class 4	Classical	Non-classical
Female sex	**2.70****(1.52–4.78)**	0.78 (0.54–1.13)	2.64 (1.70–4.10)	**1.64****(1.23–2.19)**	**1.52****(1.12–2.06)**
Age at diagnosis	0.99 (0.98–1.01)	1.00 (0.99–1.01)	1.00 (0.98–1.01)	1.00 (0.99–1.01)	0.99 (0.98–1.00)
Autoimmune disease	**1.96****(1.18–3.25)**	1.42 (0.95–2.11)	1.50 (0.98–2.28)	**0.52*****(0.39–0.68)**	**0.51*****(0.38–0.68)**
Poly-autoimmunity	0.43 (0.09–2.12)	0.61 (0.22–1.71)	**0.19****(0.05–0.76)**	1.79 (0.69–4.64)	1.02 (0.39–3.08)
Infertility or recurrent abortion	1.01 (0.50–2.04)	0.78 (0.50–1.34)	1.11 (0.64–1.92)	1.59 (0.95–2.66)	**2.65*****(1.59–4.45)**
Dermatitis herpetiformis	*Removed for insufficient observations*	2.27 (0.77–6.70)	0.99 (0.26–3.73)	0.46 (0.21–1.00)	0.80 (0.38–1.71)
Osteoporosis	**0.33****(0.16–0.69)**	0.78 (0.51–1.21)	1.09 (0.69–1.71)	1.43 (0.98–2.10)	1.01 (0.67–1.53)
Family history of CD	1.46 (0.79–2.70)	**2.24****(1.40–3.58)**	**2.09*****(1.27–3.45)**	**0.32*****(0.25–0.43)**	**0.24*****(0.18–0.33)**
Complications	*Removed for insufficient observations*	2.59 (0.70–9.59)	2.62 (0.62–11.06)	0.71 (0.16–3.05)	**4.61***(1.23–17.21)**
Duodenum (normal appearance)	**8.11*****(4.07–16.14)**	1.21 (0.70–2.08)	0.75 (0.41–1.37)	**0.31*****(0.20–0.47)**	**0.65***(0.42–1.00)**
Duodenum (Plicae reduction)	**3.45*****(1.88–6.34)**	0.96 (0.60–1.50)	**0.60***(0.36–0.99)**	**0.64***(0.43–0.93)**	0.90 (0.60–1.33)
Duodenum (Plicae absence)	1.16 (0.62–2.16)	1.32 (0.87–2.01)	1.03 (0.67–1.60)	1.00 (0.72–1.39)	0.81 (0.57–1.16)
Corazza-Villanacci B2	**9.12****(1.86–44.63)**	0.64 (0.32–1.30)	1.16 (0.49–2.77)	0.64 (0.34–1.21)	1.39 (0.67–2.91)

The bold ones are significant, where "***" indicates a P-Value<0.001, "**" a P-Value<0.01 and "*" corresponds to a P-Value<0.05.

More in depth, the LCA identified four subtypes. Class 1 is characterised by predominant lower gastrointestinal symptoms (e.g., diarrhoea, abdominal pain, meteorism) that largely overlap with the classical CD presentation as defined by the Oslo criteria. Class 2 instead is characterised by upper gastrointestinal manifestations, especially dyspepsia and gastroesophageal reflux disease. Notably, this group was more likely to include female patients and to exhibit autoimmune comorbidities, as confirmed by the MLR (female sex OR 2.7 and autoimmune disease OR 1.96). Class 3 comprised mainly of asymptomatic individuals or those with nonspecific symptoms. This class was the largest, underscoring that many patients do not fit the conventional symptomatic profile despite having biopsy-confirmed CD. Finally, Class 4 was dominated by features of microcytic anaemia and asthenia, with occasional concurrent symptoms. Interestingly, while this Class was prominent in the overall model, it was not detected in the male subgroup, suggesting sex-based differences in CD presentation.

Our study has shed some potential novel insights into the clinical presentation of CD. Indeed, although there is partial concordance between the LCA-derived Classes and the traditional Oslo categories, our findings reveal some critical discrepancies. For instance, several patients without overt gastrointestinal symptoms (Classes 3 and 4) were still classified as “classical” CD by the Oslo system. This mismatch suggests that the current clinical classifications may oversimplify the disease spectrum and could lead to under-recognition of certain phenotypes that might be at risk for specific complications, for example those caused by nutrient malabsorption [1,2,7]. In addition, it is important to note that our findings reflect the clinical experience of several Italian referral centres, which may have introduced an over-representation of specific symptoms or conditions. Nonetheless, the LCA identified four distinct and internally coherent Classes whose may be independent of the actual reason of CD diagnosis. The observed discrepancies with the Oslo classification further suggest that symptom clustering is not as straightforward or consistent. As such, these LCA-derived Classes, like the Oslo classification, are not intended to guide CD diagnosis but rather offer a clinically relevant framework for characterising patient presentations.

The MLR analysis was employed to validate the latent class subtypes derived from LCA and to assess the relationships between these new classes and additional clinical, histological, and autoimmune variables. The results of the MLR provided significant insights into the factors associated with each latent class and helped identify clinical features that differentiate the various subtypes of CD. For example, patients in Class 2, who display a significant association with autoimmune diseases and particular histological features (apparently normal duodenal aspect, but B2 Corazza-Villanacci histology), might benefit from more targeted diagnostic and therapeutic strategies. These insights reflect the success of similar AI-driven approaches in disorders such as irritable bowel syndrome, where latent class analysis has led to the identification of clinically relevant clusters that inform personalised interventions [10, 11].

The analysis also revealed that female sex was strongly associated with the higher likelihood of belonging to Class 2 (upper gastrointestinal manifestations) and Class 4 (microcytic anaemia with asthenia). In Class 2, female sex had an OR of 2.7, indicating that women were significantly more likely to experience upper gastrointestinal symptoms such as dyspepsia and gastroesophageal reflux disease compared to those in Class 1, who presented predominantly with lower gastrointestinal

symptoms. This aligns with the literature, which suggests that CD may present with more diverse manifestations in females compared to males. Class 4, primarily consisting of individuals with anaemia and fatigue, also showed a marked female predominance. Additionally, autoimmune comorbidities such as autoimmune thyroid disease, type 1 diabetes, and psoriasis were more frequently observed in Class 2 (upper GI symptoms). The OR of autoimmune diseases for Class 2 was 1.96 highlighting the strong association between upper GI manifestations and the presence of other autoimmune conditions in CD patients. This finding is consistent with existing studies suggesting that CD often coexists with other autoimmune disorders, and the association may indicate an underlying immune dysregulation that drives both the development of CD and the onset of other autoimmune conditions.

The histological damage, measured by the Corazza-Villanacci classification, was most significantly associated with Class 2 (upper gastrointestinal symptoms). Specifically, B2-type histology (which denotes more severe villous atrophy) was strongly linked to this class (OR 9.12). This suggests that individuals in Class 2, who presented with upper gastrointestinal symptoms, were more likely to have advanced histological changes in the duodenum compared to other CD subtypes. This finding is important because it underscores the clinical relevance of histological grading in CD diagnosis and highlights that individuals with more severe histological damage may not always present with the classic symptoms of malabsorption, such as weight loss or diarrhoea.

In contrast, Class 1 (lower gastrointestinal symptoms) and Class 3 (asymptomatic or nonspecific cases) did not exhibit as strong associations with histological damage, further reinforcing the idea that CD can manifest in diverse ways, and histological severity does not correlate with the extent of clinical symptoms, as already reported in a previous study [17]. The absence of clear upper gastrointestinal manifestations in Class 1 supports the notion that different clinical patterns in CD could be linked to different pathophysiological processes, such as immune-mediated damage or other factors that are not fully captured by histological analysis alone. For example, a certain association between CD and gastroesophageal reflux disease has been noticed, and factors such as dietary antigens and duodenal eosinophilic infiltration may play a role in some patients [18].

Moreover, the MLR model provided valuable insight into misclassification issues. For instance, patients with Class 3 (asymptomatic or non-predominant symptoms) who were traditionally classified as classical CD in the Oslo classification were found to have lower odds of being misdiagnosed when using the new latent classes. This suggests that the LCA-based classification may help improve the recognition of atypical or subclinical forms of CD that might otherwise be overlooked under traditional diagnostic criteria. Also, MLR analysis revealed that individuals in the non-classical CD category were more likely to belong to Class 2, characterised by upper gastrointestinal symptoms, and Class 4, characterised by microcytic anaemia. Notably, the Oslo classification's broader categories were less specific compared to the subtypes derived by LCA, which allows for more nuanced distinctions based on clinical presentations and associated comorbidities.

Despite these preliminary insights, many limitations should be noted. The retrospective nature of the study and the reliance on pre-collected data may introduce some biases. As the cohort was drawn exclusively from Italian centres, the generalisability of these findings to other populations requires further validation. Additionally, the classification according to the Oslo criteria was not centrally reviewed; however, this is also a strength, since this reflects local clinical practice. Also, a more granular analysis about the potential differences between north and south Italy or across the different enrolling centres could not be made due to the limited sample size. Finally, although the LCA model was optimised using the Bayesian information criterion, prospective studies are needed to assess the stability and reproducibility of these Classes. This study should therefore be considered as preliminary, and future research should focus on external validation of these subtypes in diverse populations and explore the integration of additional biomarkers, genetic data, and longitudinal outcomes to determine the prognostic significance of each Class. Moreover, leveraging AI further could enhance the precision of CD classification and ultimately improve tailored treatment strategies.

5. Conclusion

To conclude, our MLR analysis confirmed the validity of the latent classes derived from LCA and revealed significant associations between clinical features, histological severity, and autoimmune comorbidities. These insights could pave the way for future studies looking at personalised approaches in the classification and management of CD, tailored to the individual's clinical profile.

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Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.05.020.

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