# Supplemental Online Content

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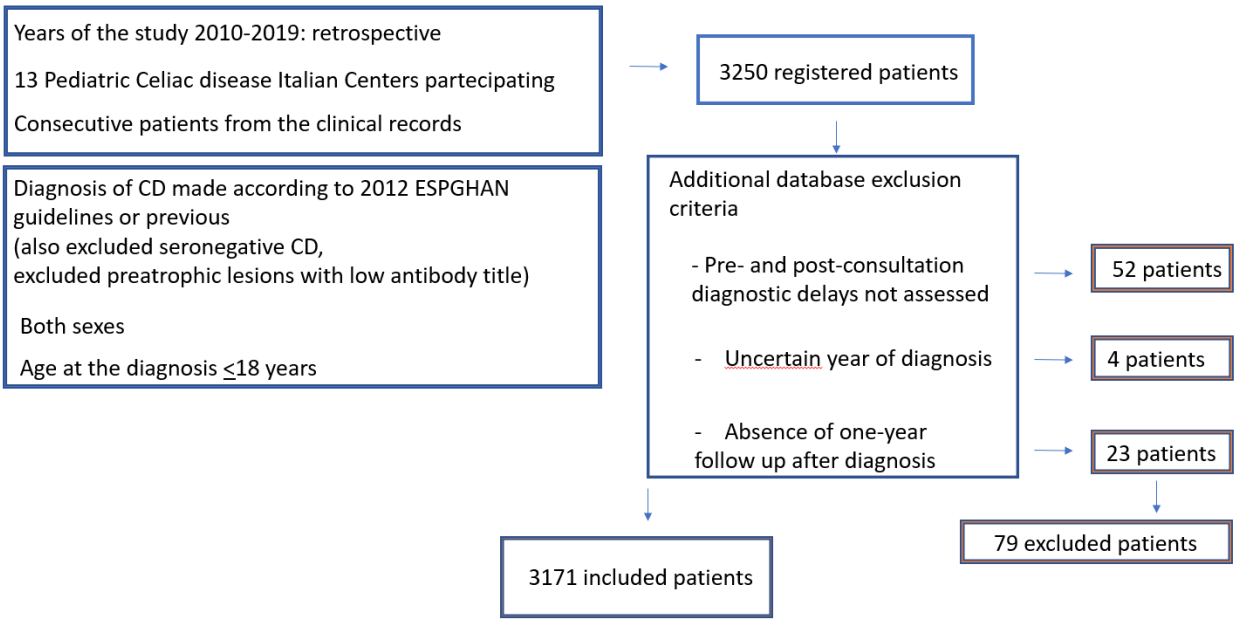
This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Pediatric celiac disease diagnostic delay: Flow chart of the inclusion and exclusion criteria of the patients.



**eMethods**

Patients' data were retrieved from the local electronic records of each participant center and transferred onto a pseudo-anonymized electronic record form. A telephone interview was also conducted to retrieve missing data, by using a standardized spreadsheet with all the variables to be collected. Each center pseudo-anonymized the data by their own numerical key. All the electronic record forms were merged and reviewed by the study coordinators (center of Pavia). The variables to be included were initially chosen by the study coordinators, and then agreed upon by all study participants. Per each center, a senior pediatrician has been involved, along with two to three consultant pediatricians. All the staff involved were expert in the diagnosis and management of CD. Hence all charts were reviewed by expert physicians, and all variables had been clearly categorized so to avoid biases. When the exact day of symptom onset was not known, this was approximated to the month of onset.

The variables collected included sociodemographic data (i.e., sex, age, ethnicity, number of siblings), clinical variables (e.g., body mass index), medical history, and a wide variety of signs or symptoms of CD (i.e., gastrointestinal symptoms, red blood cell count alterations, fatigue, associated autoimmune disorders, family history of CD, dental enamel defects, dysproteinemia, osteopenia, failure-to-thrive, delayed menarche, neuropsychiatric symptoms, dermatitis herpetiformis, selective IgA deficiency, common variable immune deficiency, Down's syndrome). The ethnicity was defined by the investigators and categorized into Asian, Black, Northern African, White. All misdiagnoses formally made by a physician made before the definitive diagnosis of CD were also recorded. When available, the duodenal histopathological lesions were reported by using the Marsh-Oberhuber classification (i.e., no lesions, Mars 0; intraepithelial lymphocytosis only, Marsh 1; crypt hyperplasia, Marsh 2; villous atrophy, Marsh 3) or the Corazza-Villanacci classification (i.e.,

non-atrophic lesions, A; Mild atrophy, B1; severe atrophy, B2).[22] The Biagi's score for assessing the adherence to a gluten free diet was also reported when available.[23]

The ethics committee of Pavia (Fondazione IRCCS Policlinico San Matteo) approved the study protocol (June 13th 2022) and this approval was extended to all the ethics committees of the other participating centers. Either the patient or the caregiver, depending on the age at the time of enrollment, were asked to sign a written informed consent to take part in the study. The necessity of a signed consent was waived for those patients who could not be reached, as all data were anonymous.

All the findings of the study conform to the STROBE standards for quality control.[24] The raw data of the study cannot be made publicly available due to privacy restrictions but can be shared by the corresponding author upon reasonable request.

*Search strategy for literature review*

We searched PubMed in September 2023, for all articles in English published since inception, using the medical subject heading terms "celiac disease" or "coeliac disease" AND "diagnostic delay", "children", "pediatric". A total of 253 entries were found with this search strategy. Two authors (MVL, PIB) reviewed all articles and included those focusing on diagnostic delay in the pediatric setting.

*Endpoints of statistical analyses and outcome definition*

The primary endpoint of the study was to determine the overall diagnostic delay, defined as the time interval between the first likely symptoms of CD, according to the available literature, and the definitive CD diagnosis. Diagnostic delay was distinguished in pre-consultation delay (i.e., the time span between the onset of symptoms and the first medical consultation) and post-consultation delay (i.e., the time span between the first medical

consultation and the definitive diagnosis). By first medical consultation we meant any assessment due to sign/symptom directly related to CD or other related clinical data (e.g., occurrence of autoimmune diseases associated with CD, other conditions related to CD, family history of CD). Assessments made in the primary care setting were also taken into account. Additionally, the secondary endpoints of the study were to describe all the possible presenting signs, symptoms, and clinical data (descriptive analysis), and looking at whether some of them were related to a greater delay or to a misdiagnosis.

*Statistical analysis*

To reach the endpoints, we retrieved data from 3000 patients. With this sample size, we were able to compute a 95% confidence interval (CI) for the median. We based this calculation as recommended on a paper by Campbell & Gardner[25], where observations are ranked, and the rank is used for the estimation of the 95% CI in our cohort; this extends from 1446 to 1555 which is sufficiently narrow. We used median and interquartile range (IQR, i.e., 25th-75th percentiles) or mean and standard deviation (SD), in case of normal distribution, to describe continuous data, while categorical data were described with counts and percentage. Percentages were calculated after the exclusion of patients with missing data when this was the case. All non-critical variables with data lacking in a percentage higher than 20% were not considered for the statistical analysis. Patients' characteristics were compared between age groups using the Cuzick's test for trend. Median overall diagnostic delay is presented in months with $25^{th}$-$75^{th}$ percentiles. Extreme diagnostic delay -overall, pre-consultation, and post-consultation- was calculated as the subgroups of patients with a diagnostic delay of more than 1.5 times the $75^{th}$ percentile.

As potential clinical data indicative of CD, we included a first-grade family history of CD, the presence of autoimmune comorbidities, dermatitis herpetiformis, selective IgA deficiency, common variable immune deficiency, and Down's syndrome. The patients were classified

according to the clinical presentation as having major (i.e., malabsorption syndrome, with diarrhea, weight loss, failure-to-thrive, nutrient and micronutrients deficiencies), minor (e.g., only isolated symptoms and single alterations, such as isolated iron deficiency anemia, unexplained osteopenia), and asymptomatic CD (i.e., completely asymptomatic and with no laboratory alterations). Potential CD was defined in case of patients with positivity to CD-specific antibodies, but absence of intestinal villous atrophy, when biopsies were taken. As per guidelines, asymptomatic patients were diagnosed by biopsy.

Univariable and multivariable logistic regression models were fitted using misdiagnoses as dependent variables and sign/symptoms/clinical data as independent variables. Parameters with $p<0.20$ at univariable analysis were included in multivariable models. The area under the model ROC curve was computed to assess discrimination. Univariable and multivariable generalized linear regression models (with gaussian family and identity link) were fitted using diagnostic delays as dependent variables and sign/symptoms/clinical data, and clinical characteristics as independent variables. Delays were log-transformed for the purpose of the analysis. Variables with $p<0.20$ at univariable analyses were included in the multivariable models. Logistic regression was used to model extreme diagnostic delays; the same variables as for the corresponding delay model were used. The statistical analyses were performed by using STATA statistical software, release 17 (StataCorp, College Station, TX). A two-sided p-value $<0.05$ was considered statistically significant.

**eTable 1.** Characteristics According to Different Age Groups

| *Variable* | *< 3 years* | *3-5 years* | *6-10 years* | *11-18 years* | *p (for trend)* |
|---|---|---|---|---|---|
| Males | 230 (19.81) | 358 (30.84) | 379 (32.64) | 194 (16.71) | 0.21 |
| Females | 420 (20.90) | 611 (30.40) | 666 (33.13) | 313 (15.57) | 0.53 |
| BMI | 15.75 (1.56) | 15.49 (1.48) | 15.89 (1.93) | 17.78 (2.07) | 0.001 |
| **Hospitalization** | 57 (8.77) | 42 (4.33) | 31 (2.97) | 20 (3.94) | 0.001 |
| **Number of diagnostic clues** | 1.09 (0.28) | 1.08 (0.27) | 1.06 (0.25) | 1.04 (0.19) | 0.74 |
| **White ethnicity, n (%)** | 639 (98.31) | 935 (96.59) | 1.018 (97.51) | *501 (99.01)* | 0.26 |
| **Multiple symptoms** | 254 (39.08) | 263 (27.14) | 267 (25.55) | 118 (23.27) | <0.001 |
| **Sum of symptoms** | 2.37 (1.59) | 1.85 (1.45) | 1.78 (1.38) | 1.70 (1.45) | <0.001 |
| **Number of g.i. symptoms** | 1.44 (1.22) | 1.01 (1.03) | 1.04 (1.02) | 0.90 (1.03) | <0.001 |
| **Gastrointestinal symptoms (at least 1), n (%)** | | | | | |
| >1 symptom | 255 (39.23) | 246 (25.39) | 275 (26.32) | 109 (21.50) | <0.001 |
| Abdominal pain | 112 (17.23) | 289 (29.82) | 439 942.01) | 185 (36.49) | <0.001 |
| Diarrhea | 286 (44.00) | 167 (17.23) | 139 (13.30) | 84 (16.57) | <0.001 |
| Bloating | 136 (20.92) | 131 (13.52) | 107 (10.24) | 41 (8.09) | <0.001 |
| Constipation | 80 (12.31) | 134 (13.83) | 143 (13.68) | 39 (7.69) | 0.002 |
| Weight loss | 120 (18.46) | 83 (8.57) | 75 (7.18) | 34 (6.71) | <0.001 |
| Anorexia | 75 (11.54) | 86 (8.88) | 73 (6.99) | 18 (3.55) | <0.001 |
| Vomiting | 92 (14.15) | 55 (5.68) | 46 (4.40) | 21 (4.14) | <0.001 |
| Dyspepsia | 24 (3.69) | 16 (1.65) | 29 (2.78) | 18 (3.55) | 0.04 |
| GERD | 6 (0.92) | 6 (0.62) | 14 (1.34) | 6 (1.18) | 0.40 |
| **Red blood cell count alteration (at least 1), n (%)** | 161 (25.00) | 280 (29.02) | 192 (18.50) | 103 (20.36) | <0.001 |
| Microcytic anemia | 147 (91.30) | 262 (93.57) | 181 (94.27) | 97 (94.17) | |
| Normocytic anemia | 12 (7.45) | 14 (5.00) | 6 (3.13) | 3 (2.91) | |
| Macrocytic anemia | 0 (0.00) | 2 (0.71) | 2 (1.04) | 2 (1.94) | |
| Neutropenia | 0 (0.00) | 1 (0.36) | 2 (1.04) | 1 (0.97) | |
| Thrombocytopenia | 2 (1.24) | 1 (0.36) | 0 (0.00) | 0 (0.00) | |
| **Recent gastrointestinal infection, n (%)** | 71 (10.92) | 54 (5.63) | 40 (3.85) | 19 (10.78) | <0.001 |
| **Fatigue** | 62 (9.57) | 114 (11.76) | 146 (14.00) | 114 (22.53) | <0.001 |
| **Associated autoimmune disorders (at least 1), n (%)** | 37 (5.75) | 52 (5.39) | 82 (7.88) | 61 (12.03) | <0.001 |
| **Family history of CD** | 140 (21.64) | 260 (26.92) | 262 (25.10) | 127 (25.15) | 0.12 |
| **Dental enamel defect** | 3 (0.47) | 11 (1.15) | 24 (2.32) | 19 (3.78) | <0.001 |
| **Dysproteinemia** | 38 (5.89) | 9 (0.94) | 6 (0.58) | 2 (0.40) | <0.001 |
| **Osteopenia** | 0 (0.00) | 7 (0.77) | 16 (1.60) | 21 (4.25) | <0.001 |
| **Failure-to-thrive** | 271 (41.82) | 333 (34.40) | 275 (26.37) | 73 (14.40) | <0.001 |
| **Neuropsychiatric symptoms** | 72 (11.11) | 75 (7.77) | 132 (12.66) | 84 (16.60) | <0.001 |
| Headache | 4 (80.00) | 8 (80.00) | 50 (98.04) | 27 (87.10) | <0.03 |
| **Dermatitis herpetiformis** | 10 (1.54) | 21 (2.17) | 21 (2.01) | 14 (2.78) | 0.53 |
| **Selective IgA deficiency** | 28 (4.31) | 15 (1.55) | 14 (1.34) | 6 (1.19) | <0.001 |
| **Common variable immunodeficiency** | 5 (0.77) | 1 (0.10) | 2 (0.19) | 0 (0.00) | 0.047 |
| **Down's syndrome** | 1 (0.15) | 1 (0.10) | 3 (0.29) | 1 (0.20) | 0.94 |
| **Biagi's GFD adherence score (1-4): mean (sd)** | 3.67 (0.59) | 3.74 (0.50) | 3.67 (0.55) | 3.62 (0.65) | 0.68 |
| **Diagnosis made by screening** | 67 (10.31) | 164 (16.92) | 201 (19.23) | 115 (22.68) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| **Diagnosis made for clinical evidence** | 528 (81.23) | 657 (67.80) | 704 (67.37) | 304 (59.96) | <0.001 |
| **Previous misdiagnosis** | 20 (3.19) | 40 (4.25) | 40 (3.93) | 24 (4.84) | 0.54 |
| **HLA DQ2 homozygosis** | 123 (32.54) | 184 (32.97) | 188 (35.01) | 85 (37.61) | 0.48 |
| **TTG IgA title > 10x ULN** | 507 (79.84) | 674 (71.02) | 654 (64.24) | 305 (61.99) | <0.001 |
| **EMA positivity** | 503 (94.91) | 745 (95.27) | 815 (94.33) | 386 (94.76) | 0.79 |
| **AGA IgG title > 10x ULN** | 144 (48.81) | 162 (51.76) | 165 (58.72) | 64 (51.61) | 0.11 |
| **Endoscopic signs of CD** | 130 (78.78) | 268 (79.76) | 436 (78.82) | 179 (77.83) | 0.35 |
| **Corazza-Villanacci A (pre-atrophic histological lesions)** | 26 (10.28) | 45 (8.38) | 41 (5.85) | 22 (6.06) | 0.005 |
| **Clinical classification** | | | | | <0.001 |
| Major | 433 (67.45) | 475 (49.63) | 436 (42.21) | 206 (40.95) | |
| Minor | 134 (20.87) | 296 (30.93) | 378 (36.59) | 171 (34.00) | |
| Asymptomatic | 55 (8.57) | 153 (15.99) | 191 (18.49) | 109 (21.67) | |
| Potential | 20 (3.12) | 33 (3.45) | 28 (2.71) | 17 (3.38) | |
| **Physician who made the diagnosis** | | | | | <0.001 |
| General pediatrician | 204 (31.38) | 321 (33.13) | 365 (34.93) | 122 (24.06) | |
| Hospital pediatrician | 372 (22.30) | 528 (54.65) | 526 (50.33) | 242 (47.73) | |
| Gastroenterologist | 55 (16.57) | 84 (8.67) | 119 (11.39) | 74 (14.60) | |
| Other specialist | 19 (11.95) | 36 (22.64) | 35 (22.01) | 69 (43.40) | |
| **Pre-consultation delay** | 3.37 (4.67) | 5.16 (8.12) | 5.98 (11.13) | 6.38 (11.80) | 0.52 |
| **Post-consultation delay** | 1.73 (2.46) | 3.13 (5.27) | 3.48 (6.43) | 3.46 (8.14) | <0.001 |
| **Overall diagnostic delay** | 5.10 (5.41) | 8.27 (9.73) | 9.46 (13.28) | 9.84 (14.71) | <0.001 |

Abbreviations: AGA, anti-deamidated gliadin antibodies; CD, celiac disease; EMA, anti-endomysial antibodies;GI, gastrointestinal; GERD, gastro-esophageal reflux disease; GFD, gluten-free diet: HLA, human leukocyte antigen; n.s., non-significative; SD, standard deviation, TTG, anti-transglutaminase antibodies; ULN, upper limit of normal.

**eTable 2.** Characteristics of Patients Who Were Diagnosed With a Biopsy Compared to those Who Were Not

| | | **Biopsy performed** | **Biopsy not performed** | **Prob > \|z\|** | **Fisher's exact p** |
|---|---|---|---|---|---|
| **Total N (%)** | | 1969 (62.1) | 1202 (37.9) | | |
| **Diagnostic delay: median (IQR) (months)** | | | | | |
| Overall | | 5 (2-12) | 4 (1-10) | <0.001 | |
| Pre-consultation | | 2 (0-6) | 2 (0-6) | 0.19 | |
| Post-consultation | | 2 (0-4) | 1 (0-3) | <0.001 | |
| **BMI, mean (SD)** | | 16.02 (1.88) | 15.88 (1.87) | 0.08 | |
| **Sex** | | | | | 0.24 |
| Males (1161) | | 705 (71.7) | 456 (39.3) | | |
| Females (2010) | | 1264 (62.9) | 746 (37.1) | | |
| **Age at diagnosis (years)** | | | | | < 0.001 |
| <3 N (%) | | 289 (44.5) | 361 (55.5) | | |
| 3-5 N (%) | | 581 (60.0) | 388 (40.0) | | |
| 6-10 N (%) | | 734 (70.2) | 311 (29.8) | | |
| 11-18 N (%) | | 365 (72.0) | 142 (28.0) | | |
| **Family history of CD** | Absent | 1470 (61.9) | 903 (38.1) | | 0.53 |
| | Present | 499 (63.2) | 290 (36.8) | | |
| **Autoimmune diseases** | Absent | 1814 (62.0) | 110 (38.0) | | 0.62 |
| | Present | 148 (63.8) | 84 (36.2) | | |
| **Multiple symptoms** | Absent | 1510 (66.5) | 759 (33.5) | | <0.001 |
| | Present | 459 (50.9) | 443 (49.1) | | |
| **Multiple diagnostic clues** | Absent | 1844 (63.9) | 1042 (36.1) | | <0.001 |
| | Present | 95 (43.6) | 123 (56.4) | | |
| **Multiple GI symptoms** | Absent | 1524 (66.7) | 762 (33.3) | | <0.001 |
| | Present | 445 (50.3) | 440 (49.7) | | |
| **Blood cell count alterations** | Absent | 1529 (63.3) | 888 (36.7) | | 0.04 |
| | Present | 434 (58.97) | 302 (41.0) | | |
| **Dyspepsia** | Absent | 1911 (62.0) | 1173 (38.0) | | 0.43 |
| | Present | 58 (66.7) | 29 (33.3) | | |
| **GERD** | Absent | 1943 (61.9) | 1196 (38.1) | | 0.03 |
| | Present | 26 (81.3) | 6 (18.8) | | |
| **Diarrhea** | Absent | 1654 (66.3) | 841 (33.1) | | <0.001 |
| | Present | 315 (46.6) | 361 (53.4) | | |
| **Weight loss** | Absent | 1836 (64.2) | 1023 (35.8) | | <0.001 |
| | Present | 133 (42.6) | 179 (57.4) | | |
| **Vomiting** | Absent | 1870 (63.2) | 1087 (36.8) | | <0.001 |
| | Present | 99 (46.3) | 115 (53.7) | | |
| **Bloating** | Absent | 1760 (63.9) | 996 (36.1) | | <0.001 |
| | Present | 209 (50.4) | 206 (49.6) | | |
| **Abdominal pain** | Absent | 1330 (62.0) | 816 (38.0) | | 0.88 |
| | Present | 639 (62.3) | 386 (37.7) | | |

| | | | | | |
|---|---|---|---|---|---|
| **Anorexia** | Absent | 1836 (62.9) | 1083 (37.1) | | 0.002 |
| | Present | 133 (52.8) | 119 (47.2) | | |
| **Constipation** | Absent | 1738 (62.6) | 1037 (37.4) | | 0.11 |
| | Present | 231 (58.3) | 165 (41.7) | | |
| **Neurological symptoms** | Absent | 1741 (62.2) | 1058 (37.8) | | 0.73 |
| | Present | 222 (61.2) | 141 (38.8) | | |
| **Dysproteinemia** | Absent | 1927 (62.4) | 1163 (37.6) | | 0.09 |
| | Present | 28 (50.9) | 27 (49.1) | | |
| **Fatigue** | Absent | 1692 (62.0) | 1038 (38.0) | | 0.75 |
| | Present | 274 (62.8) | 162 (37.2) | | |
| **Osteopenia** | Absent | 1840 (62.2) | 1120 (37.8) | | 0.88 |
| | Present | 28 (63.6) | 16 (36.4) | | |
| **Failure-to-thrive** | Absent | 1480 (66.8) | 734 (33.2) | | <0.001 |
| | Present | 487 (51.2) | 465 (48.8) | | |
| **TTG title < 10x ULN** | | 812 (85.1) | 142 (14.9) | | <0.001 |
| **TTG title ≥ 10x ULN** | | 1095 (51.2) | 1045 (48.8) | | |
| **Diagnosis made by** | | | | | |
| - screening | | 396 (72.4) | 151 (27.6) | | |
| - clinical evidence | | 1276 (58.1) | 917 (41.8) | | |
| **Clinical classification** | | | | | <0.001 |
| Major | | 796 (51.4) | 754 (48.7)) | | |
| Minor | | 681 (69.6) | 298 (30.4) | | |
| Asymptomatic | | 391 (77.0) | 117 (23.0) | | |
| **Physician who made the diagnosis** | | | | | 0.021 |
| General pediatrician | | 614 (60.7) | 398 (39.3) | | |
| Hospital pediatrician | | 1065 (63.8) | 603 (36.2) | 0.66 | |
| Gastroenterologist | | 185 (55.7) | 147 (44.3) | 0.001 | |
| Other specialist | | 105 (66.0) | 54 (34.0) | 0.018 | |

Abbreviations: CD, celiac disease; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; IQR, interquartile range; N, number; SD, standard deviation; TTG, anti-tissue transglutaminase antibodies; ULN, upper limit of normal.

**eTable 3.** Univariable Analyses for Variables Studied in Extreme Diagnostic Delay of Pediatric CD

| | **Extreme overall DD, n (%)** | **Univariable analysis OR (95% CI)** | **p-value** | **Extreme pre-consulting DD, n (%)** | **Univariable analysis OR (95% CI)** | **p-value** | **Extreme post-consulting DD, n (%)** | **Univariable analysis OR (95% CI)** | **p-value** |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | | | 0.07 | | | 0.004 | | | 0.31 |
| **Males** | 185 (15.96) | 1.000 | | 187 (16.13) | 1.000 | | 229 (19.76) | 1.000 | |
| **Females** | 368 (18.34) | 1.182 (0.985-1.418) | | 400 (19.93) | 1.294 (1.088-1.539) | | 374 (18.63) | 0.930 (0.808-1.071) | |
| **Age at diagnosis (years)** | | | | | | | | | |
| **<3** | 52 (8.00) | 1.000 | | 69 (10.62) | 1.000 | | 68 (10.46) | 1.000 | |
| **3-5** | 177 (18.27) | 2.570 (1.969-3.354) | < 0.001 | 188 (19.40) | 2.027 (1.737-2.365) | < 0.001 | 190 (19.61) | 2.088 (1.888-2.308) | < 0.001 |
| **6-10** | 216 (20.67) | 2.996 (2.155-4.166) | < 0.001 | 216 (20.67) | 2.194 (1.873-2.570) | < 0.001 | 229 (21.91) | 2.402 (1.542-3.741) | < 0.001 |
| **11-18** | 108 (21.30) | 3.113 (2.415-4.011) | < 0.001 | 114 (22.49) | 2.443 (2.081-2.867) | < 0.001 | 117 (23.08) | 2.568 (1.538-4.286) | < 0.001 |
| **Family history of CD** | 101 (12.80) | 0.627 (0.475-0.829) | 0.001 | 90 (11.41) | 0.488 (0.378-0.632) | <0.001 | 139 (17.62) | 0.880 (0.630-1.229) | 0.45 |
| **Multiple symptoms** | 169 (18.74) | 1.132 (0.776-1.651) | 0.52 | 190 (21.06) | 1.258 (1.001-1.582) | 0.049 | 139 (15.41) | 0.707 (-0.460-1.087) | 0.11 |
| **Multiple diagnostic clues** | 36 (16.51) | 0.928 (0.524-1.643) | 0.80 | 36 (16.51) | 0.859 (0.488-1.514) | 0.60 | 55 (25.23) | 1.476 (-0.750-2.904) | 0.26 |
| **Multiple GI symptoms** | 152 (17.18) | 0.975 (0.778-1.222) | 0.83 | 178 (20.11) | 1.155 (0.918- | 0.22 | 151 (17.06) | 0.832 (-0.642- | 0.17 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1.454) | | | 1.079) | |
| **Blood cell count alterations** | 127 (17.26) | 0.977 (0.725-1.318) | 0.88 | 138 (18.75) | 1.014 (0.753-1.366) | 0.93 | 127 (17.26) | 0.853 (0.608-1.195) | 0.35 |
| **GI symptoms (at least one)** | 404 (19.07) | 1.420 (1.047-1.925) | 0.02 | 463 (21.85) | 2.081 (1.610-2.690) | <0.001 | 388 (18.31) | 0.867 (0.604-1.246) | 0.44 |
| **Dyspepsia** | 23 (26.44) | 1.732 (0.748-4.099) | 0.20 | 24 (27.59) | 1.706 (0.819-3.555) | 0.15 | 16 (18.39) | 0.957 (0.421-2.172) | 0.92 |
| **GERD** | 9 (28.13) | 1.867 (1.019-3.420) | 0.04 | 8 (25.00) | 1.474 (0.939-2.313) | 0.09 | 8 (25.00) | 1.422 (0.763-2.650) | 0.27 |
| **Diarrhea** | 108 (15.98) | 0.876 (0.715-1.072) | 0.20 | 133 (19.67) | 1.101 (0.796-1.523) | 0.56 | 108 (15.98) | 0.766 (0.502-1.169) | 0.22 |
| **Weight loss** | 41 (13.14) | 0.694 (0.513-0.937) | 0.02 | 52 (16.67) | 0.869 (0.724-1.043) | 0.13 | 33 (10.58) | 0.474 (0.285-0.788) | 0.004 |
| **Vomiting** | 26 (12.15) | 0.638 (0.388-1.049) | 0.08 | 31 (14.49) | 0.732 (0.399-1.342) | 0.31 | 34 (15.89) | 0.791 (0.427-1.465) | 0.46 |
| **Bloating** | 66 (15.90) | 0.881 (0.532-1.460) | 0.62 | 84 (20.24) | 1.137 (0.712-1.814) | 0.59 | 57 (13.73) | 0.643 (0.452-0.915) | 0.01 |
| **Abdominal pain** | 218 (21.27) | 1.460 (1.243-1.716) | <0.01 | 243 (23.71) | 1.628 (1.264-2.096) | <0.001 | 208 (20.29) | 1.125 (0.963-1.314) | 0.14 |
| **Anorexia** | 49 (19.44) | 1.157 (0.849-1.576) | 0.36 | 48 (19.05) | 1.039 (0.917-1.177) | 0.55 | 38 (15.08) | 0.738 (0.493-1.105) | 0.14 |
| **Constipation** | 77 (19.44) | 1.166 (0.942-1.443) | 0.16 | 85 (21.46) | 1.238 (0.997-1.535) | 0.05 | 90 (22.73) | 1.294 (0.991-1.689) | 0.06 |
| **Neurological symptoms** | 78 (21.49) | 1.353 (1.029-1.777) | 0.03 | 77 (21.21) | 1.217 (1.007-1.471) | 0.04 | 71 (19.56) | 1.039 (0.670-1.610) | 0.87 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Dental enamel defects** | 13 (22.81) | 1.401 (0.752-2.612) | 0.29 | 12 (21.5) | 1.173 (0.498-2.762) | 0.71 | 11 (19.30) | 1.011 (0.652-1.567) | 0.96 |
| **Dysproteinemia** | 5 (9.09) | 0.469 (0.132-1.669) | 0.24 | 6 (10.91) | 0.537 (0.150-1.921) | 0.34 | 3 (5.45) | 0.242 (0.039-1.508) | 0.13 |
| **Fatigue** | 82 (18.81) | 1.114 (0.702-1.766) | 0.65 | 91 (20.87) | 1.191 (0.934-1.519) | 0.16 | 71 (16.28) | 0.802 (0.570-1.129) | 0.21 |
| **Osteopenia** | 6 (13.64) | 0.724 (0.496-1.056) | 0.09 | 8 (18.18) | 0.965 (0.541-1.721) | 0.90 | 7 (15.91) | 0.762 (0.300-1.931) | 0.57 |
| **Failure-to-thrive** | 215 (22.58) | 1.619 (1.309-2.002) | <0.001 | 246 (25.84) | 1.921 (1.706-2.162) | <0.001 | 175 (18.38) | 0.937 (0.699-1.313) | 0.71 |
| **Marsh 0-1-2** | 31 (18.45) | 1.000 | 0.80 | 27 (16.07) | 1.000 | 0.25 | 44 (26.19) | 1.000 | 0.63 |
| **Marsh 3A-3B-3C** | 350 (19.43) | 1.066 (0.646-1.759) | | 335 (18.60) | 1.193 (0.884-1.610) | | 398 (22.10) | 0.799 (0.323-1.980) | |
| **TTG title < 10x ULN** | 209 (21.91) | 1.000 | 0.07 | 177 (18.55) | 1.000 | 0.98 | 254 (26.62) | 1.000 | 0.03 |
| **TTG title ≥ 10x ULN** | 333 (15.56) | 0.657 (0.420-1.028) | | 396 (18.50) | 0.997 (0.735-1.351) | | 342 (15.98) | 0.524 (0.293-0.938) | |
| **Clinical classification** | | | | | | | | | |
| Major | 294 (18.97) | 1.000 | | 353 (22.77) | 1.000 | | 248 (16.00) | 1.000 | |
| Minor | 186 (19.00) | 1.002 (0.662-1.516) | 0.99 | 178 (18.18) | 0.754 (0.543-1.046) | 0.09 | 228 (23.29) | 1.594 (1.026-2.477) | 0.04 |
| Asymptomatic | 45 (8.86) | 0.415 (0.225-0.768) | 0.005 | 33 (6.50) | 0.236 (0.113-0.492) | <0.001 | 90 (17.72) | 1.130 (0.557-2.296) | 0.74 |
| Potential | 19 (19.39) | 1.027 (0.382-2.762) | 0.96 | 15 (15.31) | 0.613 (0.243-0.373) | 0.30 | 24 (24.49) | 1.703 (0.568-5.106) | 0.34 |
| **Physician who made** | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|
| **the diagnosis** | | | | | | | | | |
| General pediatrician | 168 (16.60) | 1.000 | | 181 (17.89) | 1.000 | | 207 (20.45) | 1.000 | |
| Hospital pediatrician | 281 (16.85) | 1.018 (0.595-1.740) | 0.95 | 281 (16.85) | 0.930 (0.677-1.277) | 0.66 | 328 (19.66) | 0952 (0.481-1.884) | 0.89 |
| Gastroenterologist | 78 (23.49) | 1.543 (0.972-2.450) | 0.07 | 86 (25.90) | 1.605 (1.199-2.149) | 0.001 | 42 (12.65) | 0.563 (0.211-1.502) | 0.25 |
| Other specialist | 26 (16.35) | 0.982 (0.553-1.744) | 0.95 | 39 (24.53) | 1.492 (1.072-2.078) | 0.018 | 27 (16.98) | 0.795 (0.343-1.846) | 0.59 |

Abbreviations: CD, celiac disease; CI, confidence interval; DD, diagnostic delay; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; N, number; OR, odds ratio; TTG, anti-tissue transglutaminase antibodies; ULN, upper limit of normal.

**eTable 4.** Univariable and Multivariable Analyses for Factors Correlated to Misdiagnosis Previous to Celiac Disease Diagnosis

| | **No misdiagnosis, n (%)** | **Misdiagnosis, n (%)** | **Univariable analysis OR (95% CI)** | **p-value** | **Multivariable analysis OR (95% CI) Area under ROC curve 0.7450 (95%CI 0.7242-0.7650)** | **p-value** |
|---|---|---|---|---|---|---|
| **Total** | 2958 (95.98) | 124 (4.02) | | | | |
| **Sex** | | | | 0.15 | | |
| **Males** | 1076 (95.39) | 52 (4.61) | 1.000 | | | |
| **Females** | 1878 (96.31) | 72 (3.69) | 0.793 (0.579-1.086) | | | |
| **Age at diagnosis (years)** | | | | 0.54 | | |
| **<3** | 607 (96.81) | 20 (3.19) | 1.000 | | | |
| **3-5** | 902 (95.75) | 40 (4.25) | 1.346 (0.847-2.138) | 0.21 | | |
| **6-10** | 977 (96.07) | 40 (3.93) | 1.243 (0.537-2.878) | 0.61 | | |
| **11-18** | 472 (95.16) | 24 (4.84) | 1.543 (0.694-3.432) | 0.29 | | |
| **Family history of CD** | 746 (97.26) | 21 (2.74) | 0.602 (0.371-0.977) | 0.040 | 0.762 (0.452-1.286) | 0.31 |
| **Multiple symptoms** | 812 (93.33) | 58 (6.67) | 2.323 (1.196-4.509) | 0.013 | | |
| **Multiple diagnostic clues** | 207 (97.18) | 6 (2.82) | 0.719 (0.495-1.046) | 0.09 | | |
| **Multiple GI symptoms** | 797 (93.99) | 51 (6.01) | 1.894 (0.796-4.506) | 0.15 | | |
| **Blood cell count alterations** | 674 (94.00) | 43 (6.00) | 1.809 (0.826-3.962) | 0.14 | 2.118 (0.954-4.700) | 0.07 |
| **Dyspepsia** | 78 (90.70) | 8 (9.30) | 2.546 (0.731-8.873) | 0.14 | 2.893 (0.951-8.794) | 0.06 |
| **GERD** | 27 (84.38) | 5 (15.63) | 4.561 (2.078-10.010) | <0.001 | 3.907 (1.955-7.811) | <0.001 |
| **Diarrhea** | 620 (94.66) | 35 (5.34) | 1.483 (0.983-2.237) | 0.06 | 2.031 (1.222-3.376) | 0.006 |
| **Weight loss** | 284 (95.95) | 12 (4.05) | 1.009 (0.621-1.639) | 0.97 | | |
| **Vomiting** | 197 (95.63) | 9 (4.37) | 1.097 (0.567-2.122) | 0.78 | | |
| **Bloating** | 370 (93.67) | 25 (6.33) | 1.766 (1.079-2.893) | 0.02 | 1.439 (1.080-1.918) | 0.01 |
| **Abdominal pain** | 942 (94.67) | 53 (5.33) | 1.598 (1.211-2.107) | 0.001 | 1.455 (1.086-1.949) | 0.01 |
| **Anorexia** | 225 (95.74) | 10 (4.26) | 1.065 (0.496-2.288) | 0.87 | | |
| **Constipation** | 353 (92.41) | 29 (7.59) | 2.253 (0.795-6.387) | 0.13 | 4.659 (2.148-10.103) | <0.001 |
| **Neurological symptoms** | 325 (92.07) | 28 (7.93) | 2.356 (1.567-3.542) | <0.001 | 1.301 (0.879-1.925) | 0.19 |
| **Dental enamel defects** | 48 (90.57) | 5 (9.43) | 2.518 (1.031-6.152) | 0.043 | 1.189 (0.300-4.707) | 0.81 |
| **Dysproteinemia** | 50 (94.34) | 3 (5.66) | 1.444 (0.553-3.768) | 0.45 | | |
| **Fatigue** | 401 (93.26) | 29 (6.74) | 1.943 (1.351-2.796) | <0.001 | 1.964 (1.515-2.545) | <0.001 |
| **Osteopenia** | 39 (97.50) | 1 (2.50) | 0.578 (0.261-1.281) | 0.18 | 0.511 (0.238-1.096) | 0.08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Failure-to-thrive** | 892 (96.33) | 34 (3.67) | 0.875 (0.620-1.233) | 0.45 | | |
| **Marsh-Oberhüber pre-atrophic histological lesions 0-1-2** | 160 (97.56) | 4 (2.44) | 1.000 | | | |
| **Marsh-Oberhüber atrophic lesions 3A-3B-3C** | 1682 (95.68) | 76 (4.32) | 1.807 (1.114-2.856) | 0.11 | 1.667 (1.147-2.424) | 0.007 |
| **TTG title < 10x ULN** | 901 (97.09) | 27 (2.91) | 1.000 | | | |
| **TTG title ≥ 10x ULN** | 1991 (95.54) | 93 (4.46) | 1.559 (1.150-2.112) | 0.004 | | |

Abbreviations: CD, celiac disease; CI, confidence interval; GERD, gastro-esophageal reflux disease; GI, gastrointestinal; N, number; OR, odds ratio; TTG, anti-tissue transglutaminase antibodies; ULN, upper limit of normal.