


ORIGINAL ARTICLE

Gastroenterology

Endoscopy and noninvasive tests in pediatric disorders of gut–brain interaction: A multicenter retrospective study of the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

Mattia Spatuzzo¹ | Chiara Imondi² | Paola De Angelis² | Fortunata Civitelli^{3,4} |
Valentina Giorgio⁵ | Caterina Strisciuglio⁶ | Renato Tambucci² |
Federica Ferrari³ | Cosimo Ruggiero¹ | Giuseppina Russo⁶ |
Danilo A. Fegatelli⁷ | Salvatore Oliva¹ 

¹Women's and Children's Health Department, Pediatric Gastroenterology and Hepatology Unit, Sapienza University of Rome, Rome, Italy

²Gastroenterology and Nutrition Unit, Bambino Gesù Children's Hospital, Rome, Italy

³Department of Gender Diseases, Child and Adolescent Health, Pediatric Unit, Sant'Eugenio Hospital, Rome, Italy

⁴Department of Translational Medicine, Gastroenterology and Hepatology Unit Sapienza University of Rome, Rome, Italy

⁵Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

⁶Department of Woman, Child and General and Specialistic Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

⁷Department of Life Sciences, Health and Health Professions, Link Campus University, Rome, Italy

Correspondence

Salvatore Oliva, Department of Maternal Infantile and Urological Sciences, "Sapienza" University of Rome, V.le Regina Elena 324, Rome 00161, Italy.
Email: salvatore.oliva@uniroma1.it

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Abstract

Objectives: Disorders of gut–brain interactions (DGBIs) are highly prevalent in pediatric gastroenterology and often lead to the use of invasive and non-invasive diagnostic tests, despite the guidance provided by the Rome IV criteria. Rome IV promotes a positive diagnostic approach based on the identification of specific symptoms occurring at defined frequencies, unexplained after thorough medical evaluation. This study aimed to evaluate the frequency and diagnostic accuracy of these tests in pediatric DGBIs.

Methods: We conducted a retrospective analysis of pediatric patients (aged 2–16 years) evaluated for suspected DGBIs, as defined by the Rome IV criteria, across five national pediatric gastroenterology centers. Patients with known underlying organic gastrointestinal diseases were excluded. Patients were grouped based on the presence or absence of “red flags” for organic pathology, including a positive family history for gastrointestinal diseases, persistent pain outside the periumbilical area, nocturnal symptoms, persistent, bilious, or bloody vomiting; presence of blood in stools or anemia; unexplained fever; altered growth parameters, delayed or abnormal puberty; associated gastrointestinal or extraintestinal symptoms; and abnormal physical findings. Clinical data, final diagnoses, and all performed tests were recorded. Statistical analysis assessed the frequency and diagnostic accuracy of each test, and a multivariate model developed to improve diagnostic accuracy.

Results: We included 500 patients with suspected DGBIs from five centers: 52.5% were female, and the median age was 9.1 ± 4.5 years. Red flags were present in 45% of patients, showing a higher frequency of positive family history, elevated inflammatory serological markers, and fecal calprotectin (FC) levels. Patients with red flag underwent more endoscopies; however, no significant increase in the detection of organic disease was observed. No single test alone demonstrated sufficient accuracy in predicting organic pathology.

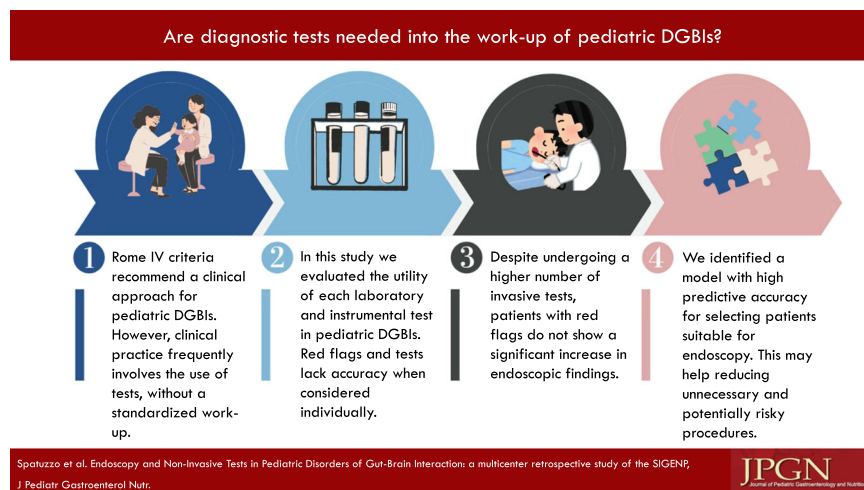
Mattia Spatuzzo and Chiara Imondi contributed equally.

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A multivariate model combining the presence of red flags, positive family history, elevated serum platelet count, and increased FC achieved the highest accuracy (area under the curve: 0.711, 95% confidence interval: 0.63–0.79).

Conclusions: A model combining red flags for organic disease, positive family history, elevated serum platelet count, and increased FC may aid in the identification of organic diseases in children with suspected DGBIs. Prospective studies are needed to validate this model and to support the diagnostic process when Rome IV criteria alone do not distinguish between organic and functional disorders.



KEYWORDS

pediatric DGBIs, red flags, Rome IV criteria

1 | INTRODUCTION

Disorders of gut–brain interactions (DGBIs) are common in the pediatric population. They refer to a group of conditions with a wide spectrum of manifestations, characterized by gastrointestinal dysmotility, visceral hypersensitivity, microbiome alterations, mast cell involvement, altered central nervous system processing, and local mucosal changes.¹ However, their exact pathophysiology remains incompletely understood.²

The conceptual framework for DGBIs has evolved from a psychosomatic to a biopsychosocial model, acknowledging psychological and social influences.^{3,4} To support clinical diagnosis, the Rome Committee developed criteria specifying necessary symptoms and recurrence intervals for each disorder (Figure 1).⁵ According to Rome IV criteria, DGBIs are grouped into three main categories: functional nausea and vomiting disorders, functional abdominal pain disorders (e.g., irritable bowel syndrome [IBS], functional dyspepsia), and functional defecation disorders (e.g., constipation, fecal incontinence).

Although Rome IV promotes a symptom-based diagnosis¹, clinical practice often focuses on excluding alarm signs of organic disease. The presence of red flags precludes a purely functional diagnosis and requires further work-up.

Several challenges underscore the need for focused research in pediatric DGBIs. First, DGBIs represent one of the most common reasons for pediatric gastroenterology consultations, with global estimates suggesting that more than 25% of children fulfill diagnostic criteria.^{6,7} Second, despite recommendations supporting a symptom-based approach, clinical practice often includes extensive diagnostic testing, which can cause unnecessary discomfort and increased costs.⁸ Moreover, there is no standardized diagnostic pathway, leading to inconsistent management and potential overuse of invasive procedures. Third, the economic burden is significant: UK data estimate annual management costs for pediatric DGBIs at £73 million,⁹ while US estimates suggest over \$11,787 per adolescent annually, excluding indirect costs such as missed school or parental work absenteeism.¹⁰

In this multicenter retrospective study, promoted by the Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP), we aimed to evaluate the diagnostic utility of key clinical, laboratory, and imaging tests in pediatric DGBIs. Primary goals were to assess the frequency of organic versus functional diagnoses and determine the diagnostic accuracy of clinical history, labs, and imaging. Finally, we aimed to build a multivariate logistic model combining clinical

and laboratory variables to guide appropriate use of invasive investigations.

2 | METHODS

2.1 | Ethics statement

The study was approved by the Ethics Committee of Policlinico Umberto I, Rome, which served as the coordinating center (Protocol No. 0045/2025).

2.2 | Study design and population

This retrospective, multicenter observational study included pediatric patients aged 2–16 years evaluated for suspected DGBIs, according to Rome IV criteria, between January 2020 and May 2022. Patients younger than 2 years or older than 16 years, those with known organic disease, or presenting for unrelated conditions were excluded (Figure S1).

2.3 | Participating centers

Five Italian pediatric referral centers participated: Policlinico Umberto I in Rome; Bambino Gesù Children's Hospital in Rome; Gemelli University Hospital Foundation in Rome; Sant' Eugenio Hospital in Rome; and the University of Campania "Luigi Vanvitelli" in Naples. Inclusion criteria were age eligibility and clinical suspicion of DGBIs according to Rome IV criteria (Figure 1). Patients with known gastrointestinal diseases (e.g., food allergies) were excluded (Figure S1).

2.4 | Red flags

Patients were stratified based on the presence of red flags for organic pathology, defined according to Rome IV: family history of gastrointestinal (GI) disease, persistent pain localized outside the periumbilical region, particularly in the right quadrants, nocturnal symptoms, persistent or bilious vomiting, hematemesis or blood in stools, anemia, unexplained fever, growth failure, delayed puberty, dysphagia, perianal disease, arthritis, or palpable masses.

2.5 | Data collection

In both groups, collected data included demographics, clinical features, anthropometric measurements, suspected diagnoses, diagnostic tests, comorbidities, therapies, and final diagnoses.

What is Known

- The Rome IV criteria recommend a positive diagnostic approach for disorders of gut–brain interactions (DGBIs); however, clinical practice frequently involves laboratory and instrumental testing of uncertain utility.
- No standardized diagnostic work-up currently exists for DGBIs.
- Patients with DGBIs often undergo unnecessary invasive endoscopic procedures, increasing the diagnostic burden on patient and their families. This practice may also detract from a necessary psychosomatic approach to care.

What is New

- We evaluated the real-world application of the Rome IV criteria in Italy, assessing the utility of laboratory and instrumental tests in pediatric DGBIs.
- In our large cohort of patients with suspected DGBIs, over 80% maintained a functional diagnosis based solely on clinical history, even after diagnostic testing, supporting the Rome IV approach centered on clinical evaluation. Fewer than 20% received a final diagnosis of organic disease; among these, only two-thirds exhibited red flags at onset, suggesting that red flags alone have limited diagnostic accuracy and require integration with additional clinical and laboratory parameters.
- Despite undergoing a higher number of invasive tests, patients with red flags did not show a statistically significant increase in endoscopically confirmed organic pathology.

2.6 | Serum laboratory parameters

Laboratory values were evaluated using standard reference thresholds: hemoglobin (Hb) 12.1 g/dL and platelet count (PLT) 430.000/L. Erythrocyte sedimentation rate (ERS) and C-reactive protein (CRP) were considered pathological if >25 mm/h and 0.6 mg/dL, respectively. Fecal calprotectin (FC) values were expressed in µg/g, with a positive test defined as >150 µg/g. Celiac screening was performed using tissue-transglutaminase-immunoglobulin A (IgA), with <20 AU/mL considered negative.

Rome IV Criteria for Disorders of Gut-Brain Interaction (2016):	
Functional Nausea and Vomiting Disorders	
1. <i>Cycling Vomiting Syndrome</i> : Must include all of the following: the occurrence of 2 or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period; episodes are stereotypical in each patient; episodes are separated by weeks to months with return to baseline health between episodes; after appropriate medical evaluation, the symptoms cannot be attributed to another condition.	
2. <i>Functional Nausea</i> : Must include all of the following fulfilled for the last 2 months: bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals; not consistently associated with vomiting; after appropriate evaluation, the nausea cannot be fully explained by another medical condition	
3. <i>Functional Vomiting</i> : Must include all of the following: on average, 1 or more episodes of vomiting per week; absence of self-induced vomiting or criteria for an eating disorder or rumination; after appropriate evaluation, the vomiting cannot be fully explained by another medical condition	
4. <i>Rumination Syndrome</i> : Must include all of the following: repeated regurgitation and rechewing or expulsion of food that begins soon after ingestion of a meal; does not occur during sleep; not preceded by retching; after appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out.	
5. <i>Aerophagia</i> : Must include all of the following: excessive air swallowing; abdominal distention due to intraluminal air which increases during the day; repetitive belching and/or increased flatus; after appropriate evaluation, the symptoms cannot be fully explained by other medical conditions.	
Functional Abdominal Pain	
1. <i>Functional Dyspepsia</i> : Must include 1 or more of the following symptoms at least 4 days per month; postprandial fullness; early satiation; epigastric pain or burning not associated with defecation; after evaluation, the symptoms cannot be explained by other medical conditions.	
2. <i>Irritable Bowel Syndrome</i> : Must include all of the following: abdominal pain at least 4 days per month associated with one or more of the following: related to defecation; a change in frequency of stool; a change in form (appearance) of stool; in children with constipation, the pain does not resolve with resolution of the constipation; after appropriate evaluation, the symptoms cannot be fully explained by another medical condition.	
3. <i>Abdominal Migraine</i> : Must include all of the following occurring at least twice: paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom); episodes are separated by weeks to months; the pain is incapacitating and interferes with normal activities; stereotypical pattern and symptoms in the individual patient; the pain is associated with 2 or more of the following: anorexia, nausea, vomiting, headache, photophobia, pallor, after appropriate evaluation, the symptoms cannot be fully explained by another medical condition.	
4. <i>Functional Abdominal Pain - not otherwise specified</i> : Must be fulfilled at least 4 times per month and include all of the following: episodic or continuous abdominal pain that does not occur solely during physiologic events (eg, eating, menses); insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine; after appropriate evaluation, the abdominal pain cannot be fully explained by other medical conditions.	
Functional Defecation Disorders	
1. <i>Functional Constipation</i> : Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome: 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years; at least 1 episode of fecal incontinence per week; history of retentive posturing or excessive volitional stool retention; history of painful or hard bowel movements; presence of a large fecal mass in the rectum; history of large diameter stools that can obstruct the toilet	
1. <i>Fecal Incontinence</i> : At least a 1-month history of the following symptoms in a child with a developmental age older than 4 years: defecation into places inappropriate to the socio-cultural context; no evidence of fecal retention; after appropriate medical evaluation, the fecal incontinence cannot be explained by another medical condition	

FIGURE 1 Rome IV criteria for the clinical diagnosis of DGBIs (2016). DGBIs, disorders of gut-brain interactions.

2.7 | Instrumental tests

Abdominal ultrasound and digestive endoscopy were performed across centers. Biopsies were processed per national guidelines by experienced pathologists.

2.8 | Primary and secondary outcomes

The primary objective was to evaluate the accuracy of each test in predicting organic pathology, assessed by

receiver operating characteristic (ROC) curves for demographic variables (age, gender, family history of GI disease, and presence of red flags), laboratory indices (white blood cells [WBCs], PLT, ESR, CRP, and FC), and diagnostic tests (abdominal ultrasound, esophagogastroduodenoscopy [EGD], ileocolonoscopy). Additionally, we sought to identify the most effective combination of diagnostic and clinical variables to develop a multivariate logistic regression model aimed at improving the selection of patients for invasive procedures.

2.9 | Statistical analysis

Statistical analysis was performed using R software (v 3.5.1). chi-square tests were used for categorical variables and the Mann–Whitney *U* test (Wilcoxon rank-sum test) for continuous variables. In Table 2, results are presented as median (interquartile range) or mean (standard deviation). Area under the curve (AUC) values for ROC analysis were interpreted as follows: AUC = 0.5 not informative, $0.5 < \text{AUC} < 0.7$ low accurate, $0.7 < \text{AUC} < 0.9$ moderate accuracy, $0.9 < \text{AUC} < 1.0$ high accuracy, AUC = 1 perfect test.

3 | RESULTS

3.1 | Demographic data

Our study included 500 patients with suspected DGBIs (Figure S1): 52.5% were female and of school age, with a median age of 9.1 ± 4.5 years. Patients were divided into two groups based on the presence or absence of one or more red flags for organic pathology at initial assessment: 45% of the cohort presented at least one red flag. The frequency of red flags is detailed in Table 1.

3.2 | Initial suspicion and final diagnosis

At presentation, the most frequent clinical suspicion was functional abdominal pain not otherwise specified (FAP-NOS), especially among those with red flags (53.5%, $p < 0.001$), while functional constipation was more common in patients without red flags (46.5%, $p = 0.005$). At discharge, 81% received a confirmed DGBI diagnosis—most commonly functional constipation (42.8%) and FAP-NOS (21.7%). Only 19% were diagnosed with organic pathology, mainly peptic ulcer disease and GERD (10.8%), and just 62% of these had red flags initially ($p = 0.001$). Further details on final diagnoses are provided in Table 1.

3.3 | Comorbidities

Overall, 43% of the cohort had at least one comorbidity, most commonly allergic conditions (17.4%), neurological disorders (5.8%; $n = 29$), and headaches (4.8%; $n = 12$) (Table 1). There was no significant difference in the prevalence of comorbidities between the groups with and without red flags.

3.4 | Laboratory tests

All patients underwent laboratory investigations, including complete blood count and inflammatory markers. Celiac serology was conducted in 59% of the cohort. No significant differences emerged in CRP, Hb, or tissue-transglutaminase-IgA levels (Table 2). However, FC levels were higher in the red flag group (median 35 $\mu\text{g/g}$ vs. 15.6 $\mu\text{g/g}$; $p < 0.001$). Similar findings were observed for ERS and WBC count.

3.5 | Instrumental tests

Endoscopy was performed in 150 patients (100 EGD, 50 ileocolonoscopy), more frequently in those with red flags, though this did not correlate with more organic diagnoses ($p = 0.148$). Additional diagnostic tests were performed in 50.3% of patients, with MR-enterography, stool microbiology, and thyroid function tests showing differences between groups. Table 1 summarizes the frequency and diagnostic impact of the tests performed.

3.6 | Medical therapies

The most prescribed treatments were laxatives (47%), probiotics (32.1%), and proton pump inhibitors (PPIs) or alginates (20%). Patients with red flags received more therapies, particularly PPIs ($p < 0.01$), anti-spasmodics ($p = 0.02$), and alginates ($p = 0.035$).

3.7 | Diagnostic tests accuracy

ROC analysis of individual variables did not show sufficient accuracy for predicting organic disease (Figure 2). Therefore, a multiple logistic regression model combining clinical and laboratory variables was developed (Figure S2). The most accurate combination included red flags, FC, thrombocytosis, and family history of GI disease showed the best performance (AUC: 0.711; 95% confidence interval [CI]: 0.63–0.79). (odds ratio [OR] red flags 1.289, 95% CI: 0.749–2.170, OR PLTs 2.570, 95% CI: 1.475–4.636; OR FC 1.027, 95% CI: 1.004–1.057; OR family history of GI disease GI 2.020, 95% CI: 0.895–4.548) (Figure 2).

4 | DISCUSSION

In this multicenter retrospective study, we aimed to evaluate the utility of diagnostic tests in the work-up of pediatric DGBIs by analyzing their frequency and diagnostic accuracy. Most patients ultimately received

TABLE 1 Demographic information, presence of red flags, family history, comorbidities, diagnostic suspicion at the onset, diagnosis at discharge, and therapy.

	Overall	No red flags	Red flags	<i>p</i>
Demographic characteristics				
Number of patients	500	272	228	
Gender (Male)	237	125	112	0.563
Age at initial evaluation	9.1	8.4	10	<0.001
Diagnostic suspicion (according to Rome IV)				
Recurrent abdominal pain	43.9% (219)	35.8% (97)	53.5 (122)	<0.001
Cyclic vomiting syndrome	1.2% (6)	0.7% (2)	1.8% (4)	0.532
Functional diarrhea	12% (60)	9.2% (25)	15.4% (35)	0.05
Functional constipation	40.7 (203)	46.5% (126)	33.8% (77)	0.005
Functional nausea and vomiting	21.8% (109)	21.8% (59)	21.9% (50)	1.000
IBS	4.4% (22)	5.5% (15)	3.1% (7)	0.264
Abdominal migraine	0.6% (3)	1.1% (3)	0 (0)	0.311
Red flags (according to Rome IV)				
Localized pain	9.2% (46)	0	20.2% (46)	N.A.
Nocturnal pain	8.4% (42)	0	18.4% (42)	N.A.
Weight loss	5.2% (26)	0	11.4% (26)	N.A.
Perianal disease	1.4% (7)	0	3.1% (7)	N.A.
Dysphagia	4% (20)	0	8.8% (20)	N.A.
Persistent vomiting	1.4% (7)	0	3.1% (7)	N.A.
Growth deceleration	2.8% (14)	0	6.1% (14)	N.A.
Delayed puberty	0	0	0	N.A.
Rectal bleeding	12% (60)	0.4% (1)	25.9% (59)	N.A.
Nocturnal diarrhea	0.8% (4)	0	3.5% (8)	N.A.
Fever	1.6% (8)	0	1.8% (4)	N.A.
Family history of GI disorders	11.6% (58)	0.4% (1)	25% (57)	N.A.
Comorbidities				
Personal comorbidities (all)	42.9% (214)	41.7% (113)	44.3% (101)	0.621
Peptic ulcer disease	2% (10)	2.2% (6)	1.8% (4)	0.965
Cardiovascular diseases	2.6% (13)	3.3% (9)	1.8% (4)	0.417
Epilepsy/neurological disorders	5.8% (29)	6.3% (17)	5.3% (12)	0.773
Migraine	4.8% (24)	4.4% (12)	5.3% (12)	0.823
Allergic conditions	17.4% (87)	16.2% (44)	18.9% (43)	0.515
Rheumatological diseases	2.4% (12)	1.1% (3)	3.9% (9)	0.077
Psychiatric disorders	3.2% (16)	3.7% (10)	2.6% (6)	0.679
Obesity	1.8% (9)	1.8% (5)	1.8% (4)	1.000
Endocrine disorders	3.6% (18)	2.2% (6)	5.3% (12)	0.114
Hepato-pancreatic diseases	2.2% (11)	1.8% (5)	2.6% (6)	0.772
Renal diseases	1% (5)	0.7% (2)	1.3% (3)	0.846

TABLE 1 (Continued)

	Overall	No red flags	Red flags	p
Family history				
Family history of GI disorders (all)	29.5% (147)	20.3% (55)	40.4% (92)	<0.001
IBD	4.6% (23)	1.5% (4)	8.3% (19)	0.001
Celiac disease	5% (25)	1.1% (3)	9.6% (22)	<0.001
EOE	0.4% (2)	0 (0)	0.9% (2)	0.404
Peptic ulcer disease	10.4% (52)	8.5% (23)	12.7% (29)	0.163
Migraine	1.2% (6)	0.4% (1)	1.8% (4)	0.199
Hepato-pancreatic disorders	1% (5)	0.4% (1)	1.8% (4)	0.199
Allergic conditions	6% (30)	3.3% (9)	9.2% (21)	0.01
Diagnosis at discharge				
Functional abdominal pain	21.7% (108)	19.3% (52)	24.6% (56)	0.186
Cyclic vomiting syndrome	1.8% (9)	1.8% (5)	1.8% (4)	1.000
Functional constipation	42.8% (213)	47.4% (128)	37.3% (85)	0.029
Functional diarrhea	3.2% (16)	3.3% (9)	3.1% (7)	1.000
Functional nausea and vomiting	8% (40)	8.9% (24)	7% (16)	0.557
IBS	9.4% (47)	10% (27)	8.8% (20)	0.764
IBD	2.2% (11)	1.1% (3)	3.5% (8)	0.13
Celiac disease	1.8% (9)	1.1% (3)	2.6% (6)	0.349
GERD	10.8% (54)	8.1% (22)	14% (32)	0.048
<i>Helicobacter pylori</i> infection	1.2% (6)	1.1% (3)	1.3% (3)	1.000
Hepato-pancreatic disease	0.6% (3)	0 (0)	1.3% (3)	0.189
Abdominal migraine	0.8% (4)	0.7% (2)	0.9% (2)	0.838
Therapies				
Probiotics	32.1% (160)	34.7% (94)	28.9% (66)	0.203
Antispasmodics	14.6% (73)	11.1% (30)	18.9% (43)	0.02
Antidiarrheals	0.4% (2)	0.4% (1)	0.4% (1)	1.000
Tricyclic antidepressant	1.2% (6)	1.1% (3)	1.3% (3)	1.000
Prokinetics	2.8% (14)	2.2% (6)	3.5% (8)	1
Laxatives and stool softeners	47.3% (236)	49.8% (135)	44.3% (101)	0.254
PPIs	20.4% (102)	13.7% (37)	28.5% (65)	<0.001
Alginates	21.8% (109)	18.1% (49)	26.3% (60)	0.035
Cyproheptadine	1.2% (6)	1.1% (3)	1.3% (3)	1
Mesalazine	2.2% (11)	1.1% (3)	3.5% (8)	0.13
Antibiotics	6.8% (34)	5.9% (16)	7.9% (18)	0.483

Abbreviations: EOE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; N.A., not applicable; PPI, proton pump inhibitors.

a functional diagnosis, with diagnostic tests often confirming the initial clinical suspicion, suggesting that many investigations may be unnecessary in the absence of alarm features. Conversely, only 19% had

organic pathology, and just 62% of these showed red flags at presentation—indicating that red flags alone are not sufficiently accurate for predicting organic disease. To improve diagnostic accuracy, we explored

TABLE 2 Frequency of the use of each test in the entire cohort and between the groups with and without red flags.

	Overall	No red flags	Red flags	p
Laboratory investigations				
Total Hb (g/dL)	13.0 (12.0; 13.8)	13.0 (12.0;13.8)	12.9 (12.2; 13.7)	0.461
ERS (mm/h)	2 (0;7)	2 (0;5)	1 (0;5)	0.4
CRP (mg/dL)	0.06 (0.02; 0.2)	0.06 (0.02; 0.2)	0.07 (0.03; 0.32)	0.949
WBCs (x10 ³)	6900 (5400; 8180)	6705 (5400; 8102)	7100 (5750; 8300)	0.383
PLTs (x10 ³)	282,000 (235,000; 316,000)	280,000 (241,000; 318,000)	285,000 (228,750; 311,500)	0.065
Fecal calprotectin (µg/g)	23.9 (1; 38.3)	15.6 (1; 36.2)	35.0 (24.0; 47.2)	<0.001
Celiac screening conducted	59.3% (296)	57.6% (156)	61.4% (140)	0.436
Positive celiac screening	1.8% (9)	1.1% (3)	2.6% (6)	0.349
Instrumental investigations				
Ultrasound performed	19% (95)	22% (60)	15.4% (35)	0.07
Abnormal ultrasound findings	4.4% (22)	2.2% (6)	7% (16)	0.017
pH metry/impedance testing conducted	3% (15)	2.6% (7)	3.5% (8)	0.734
Abnormal pH metry/impedance testing	0.4% (2)	0.7% (2)	0 (0)	0.556
Performed EGD	20% (100)	12.5% (34)	28.9% (66)	<0.001
Abnormal EGD	5.6% (28)	4.1% (11)	7.5% (17)	0.148
Abnormal histology in EGD	4.6% (23)	2.6% (7)	7% (16)	0.032
Colonoscopy performed	10% (50)	4.1% (11)	17.1% (39)	<0.001
Abnormal colonoscopy findings	0.8% (4)	1.1% (3)	0.4% (1)	0.741
Abnormal histology in colonoscopy	1.6% (8)	1.5% (4)	7% (16)	1.000
Other diagnostic tests performed				
Total	50.3% (251)	46.1% (125)	55.3% (126)	0.052
Entero-MRI	2.2% (11)	0.4% (1)	4.4% (10)	0.006
Brain-MRI	1.4% (7)	1.1% (3)	1.8% (4)	0.818
Anorectal manometry	2.2% (11)	3% (8)	1.3% (3)	0.35
Esophageal manometry	0 (0)	0 (0)	0 (0)	0.054
Upper GI series (barium swallow)	2.8% (14)	2.2% (6)	3.5% (8)	0.548
Sweat chloride testing	1.2% (6)	1.5% (4)	0.9% (2)	0.842
Allergy testing	13.6% (68)	12.9% (35)	14.5% (33)	0.708
Stool culture and parasitological tests	11.8% (59)	8.9% (24)	15.4% (35)	0.036
<i>Helicobacter pylori</i> detection	11.2% (56)	10.3% (28)	12.3% (28)	0.586
Abnormal abdominal X-ray	4.6% (23)	5.2% (14)	3.9% (9)	0.665

TABLE 2 (Continued)

	Overall	No red flags	Red flags	p
Thyroid screening conducted	23.6% (118)	17.7% (48)	30.7% (70)	0.001
Lactose breath test	3.4% (17)	2.2% (6)	4.8% (11)	0.178

Note: Quantitative variables are presented as median (IQR), qualitative variables as mean (SD).

Abbreviations: CRP, C-reactive protein; EGD, esophagogastroduodenoscopy; ERS, erythrocyte sedimentation rate; GI, gastrointestinal; Hb, haemoglobin; IQR, interquartile range; MRI, magnetic resonance imaging; PLTs, platelets; SD, standard deviation; WBCs, white blood cells.

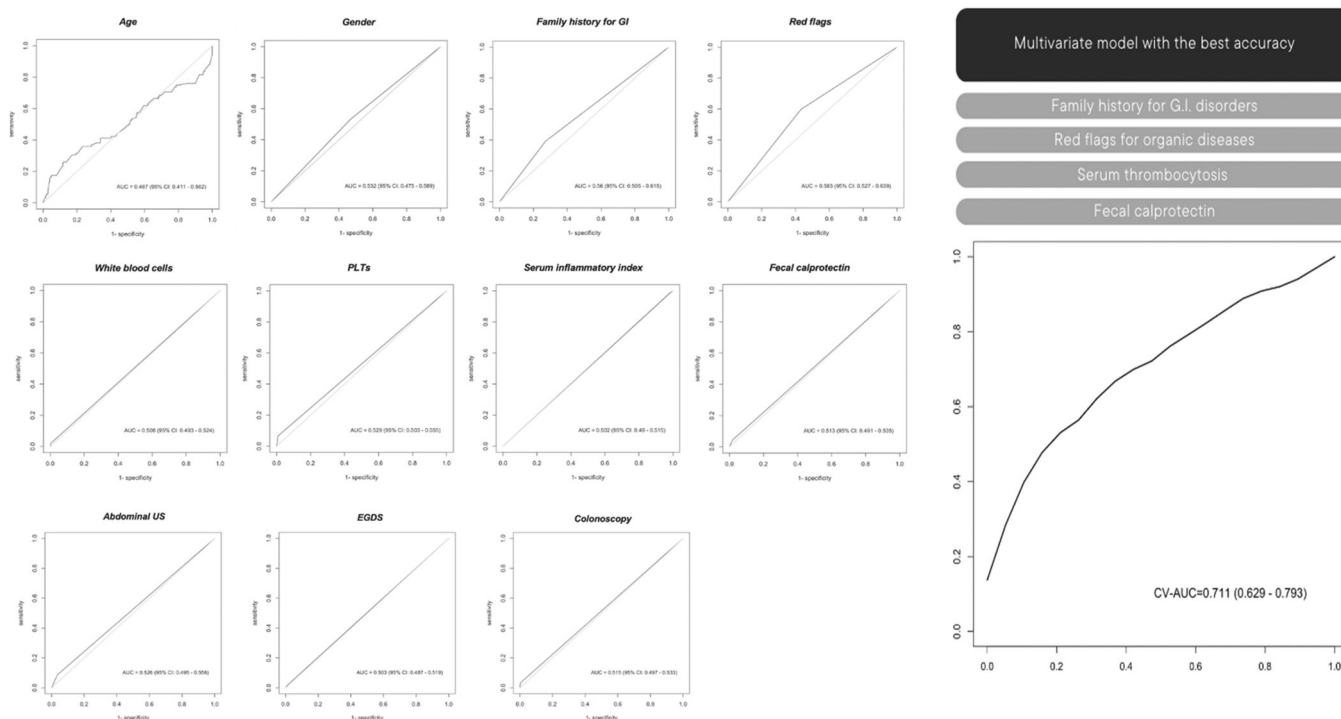


FIGURE 2 Accuracy of each diagnostic test and of the best multiple logistic combination to predict a final diagnosis for organic disease in our work. Egd, Esophagogastroduodenoscopy; GI, Gastro-intestinal; PLts, Platelets; Us, Ultrasound.

combinations of clinical features and tests. While patients with red flags more often had abnormal findings (Figure S3), no single marker reliably distinguished organic from functional disorders.

FC, a noninvasive inflammation marker, has gained attention. Though limited by handling and reference values, both ESPGHAN¹¹ and the Rome Foundation¹² recommend FC to help distinguish between functional gastrointestinal disorders and inflammatory bowel diseases (IBD). Despite the higher diagnostic performance in children compared to adults, there is no universally accepted cut-off,¹³ we used 150 µg/g, a value supported by literature as balancing sensitivity and specificity. In our cohort, FC levels alone did not differ significantly between patients with and without red flags. However, its diagnostic utility improved when combined with other clinical variables.¹⁴

Regarding *celiac screening*, previous studies show higher prevalence in children with IBS-like

symptoms.^{15,16} Based on this, Rome IV recommends screening in all children with suspected IBS.¹⁷ In our cohort, testing was frequent, particularly in suspected functional abdominal pain (73%), functional diarrhea (90%), and functional constipation (46%). However, diagnostic yield remained low, and no clinical predictors for screening emerged.

Despite literature supporting selected use^{18,19} our study found no significant differences in diagnostic yield from other tests—including abdominal ultrasound, pH-impedance, abdominal or digestive tract X-rays, manometry, breath tests, or MRI. Despite their common use, the Rome criteria do not recommend routine *abdominal ultrasound* due to its low specificity. A 2019 review highlighted its limited diagnostic value, noting it primarily serves to reassure families and clinicians.¹²

Endoscopy presents a particular challenge. ESPGHAN recommends it only in the presence of red

flags, though the evidence is limited.¹⁷ One US study found that among 290 children undergoing EGD for suspected functional symptoms, only 38% had a conclusive organic diagnosis. An Australian study similarly reported that only 10% of colonoscopies revealed organic pathology, usually in patients with prior abnormal inflammatory markers.²⁰ These findings suggest that history and noninvasive biomarkers may better identify candidates for invasive procedures. Still, endoscopy is crucial for avoiding delayed diagnoses of serious conditions such as IBD and celiac disease, which can present with functional-like symptoms. About 30%–40% of children with IBD or celiac disease initially present with functional complaints.^{21,22} Early endoscopy can expedite diagnosis and improve outcomes, particularly in children whose growth is affected. Economically, while avoiding endoscopy may seem cost-effective, repeated non-invasive testing may ultimately raise healthcare costs. Yet, as seen in previous studies, endoscopy often fails to significantly impact management in suspected DGBIs unless guided by risk stratification.^{23–25} One proposed strategy involves combining clinical and laboratory markers. For example, a risk-stratified model by Mark et al.²⁶ led to a much lower rate of organic diagnoses in low-risk patients (6%) compared to high-risk ones (34%).

Inspired by this, we aimed to identify the most effective individual test or *combination of tests* for selecting patients who might benefit from endoscopy. ROC analysis showed that no single variable had sufficient predictive value. However, multivariate analysis revealed that a combination of red flags, FC, thrombocytosis, and a positive family history of gastrointestinal disease provided the best diagnostic accuracy (AUC: 0.711; 95% CI: 0.63–0.79).

Therapeutic management showed no major differences between groups. Laxatives, PPIs, antispasmodics, alginates, and probiotics were commonly prescribed across both functional and organic diagnoses, indicating overlapping treatment strategies in clinical practice.

This study has several limitations. Its retrospective design may introduce bias, however, the large sample and inclusion of five centers reflect real-world variability. Second, a standardized diagnostic protocol was not applied across centers, however, given the lack of standardized protocols for DGBIs, our findings reflect real-world practice. Third, we did not differentiate between DGBI subtypes, although functional gastrointestinal disorders frequently overlap in pediatric patients, making strict subclassification challenging. Finally, our multivariate model has not yet been prospectively validated. To address this, we have initiated a prospective study enrolling a larger cohort of patients with suspected DGBIs.

5 | CONCLUSION

In our cohort, red flags alone were insufficient to reliably identify candidates for invasive procedures. No single first-line test predicted organic disease with high accuracy. However, a combination of red flags, family history, thrombocytosis, and elevated FC levels was associated with higher odds of organic pathology, supporting more extensive investigations in selected patients. Further prospective studies are needed to validate this approach, particularly when Rome IV criteria alone are inadequate. If confirmed, this model may help reduce unnecessary procedures while improving diagnostic efficiency in children with suspected DGBIs.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Salvatore Oliva  <https://orcid.org/0000-0003-2348-2308>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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