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Esophageal 24-Hour Multichannel Intraluminal Impedance-pH Monitoring Characteristics in Children with Gastrointestinal, Respiratory, or Chest Symptoms: A Single-Center Retrospective Cross-Sectional Study

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Highlights

What are the main findings?

- In children aged ≥1 year, abnormal report-based MII-pH classifications were more frequent among those with gastrointestinal symptoms than among those with respiratory or chest symptoms, whereas weakly acidic and proximal reflux proportions did not differ significantly between groups.
- In the exploratory infant analysis, weakly acidic reflux was significantly more frequent in those without gastrointestinal symptoms than in those with them.

What are the implications of the main findings?

- Respiratory or chest symptoms in children should not be automatically presumed to reflect underlying GERD.
- The monitoring findings alone cannot establish the benefit of empirical acid-suppressive therapy for respiratory or chest symptoms; treatment decisions should follow established pediatric guidance.

Abstract

Background: Children referred for assessment of suspected gastroesophageal reflux disease (GERD) may present predominantly with gastrointestinal, respiratory, or chest symptoms. This study compared multichannel intraluminal impedance-pH (MII-pH) reflux characteristics across these presenting-symptom groups. Methods: This single-center retrospective cross-sectional study included 202 children monitored between September 2024 and June 2026. The principal comparison included 157 children aged ≥1 year: 32 with gastrointestinal, 86 with respiratory, and 39 with chest symptoms. Forty-one infants were analyzed separately. Group comparisons used nonparametric tests, with age- and sex-adjusted median and logistic regression for continuous outcomes and abnormal monitoring classifications, respectively. Results: In the principal comparison of children aged ≥1 year, the weakly acidic reflux proportion and proximal reflux ratio did not differ between the respiratory or chest symptoms group and the gastrointestinal group. However, the proportion of abnormal classifications recorded in the original clinical reports was higher in the gastrointestinal group (84.4% vs. 32.6% vs. 38.5%, $p < 0.001$; adjusted odds ratios 0.064 and 0.093 for the respiratory or chest symptoms groups, respectively). In an exploratory analysis of the

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infant cohort, which included only seven children with gastrointestinal symptoms, the non-gastrointestinal-symptom group had a higher weakly acidic reflux proportion (83.6% vs. 62.9%, $p = 0.008$), whereas the absolute number of weakly acidic reflux events did not differ significantly (36.0 vs. 61.0, $p = 0.093$). Conclusions: Children presenting predominantly with respiratory or chest symptoms did not exhibit higher weakly acidic or proximal reflux proportions than those with gastrointestinal symptoms. Differences in abnormal report-based MII-pH classifications should be interpreted cautiously because of potential interpretation bias and should not be considered evidence of independently confirmed differences in GERD prevalence.

Keywords: gastroesophageal reflux; intraluminal impedance-pH monitoring; children; weakly acidic reflux; respiratory symptoms; chest symptoms

1. Introduction

Gastroesophageal reflux disease (GERD) refers to a condition in which gastric contents reflux into the esophagus, causing troublesome symptoms and/or complications [1]. GERD is one of the most common pediatric disorders, with a prevalence of approximately 2–8% in the general pediatric population; reflux is even more common in infants, with regurgitation symptoms occurring in about 40–50% of infants aged 1–3 months [2,3]. The typical gastrointestinal symptoms of GERD include recurrent regurgitation, vomiting, and heartburn. Children evaluated for suspected GERD may also present with respiratory symptoms, such as chronic cough, wheezing, or stridor, or with chest tightness or chest pain. However, GERD can also present with extraesophageal symptoms, including chronic cough, wheezing, stridor, chest tightness, chest pain, cyanosis, and odynophagia. Although the role of GERD in adult respiratory symptoms is widely recognized, evidence supporting this association in children remains limited [4].

It is currently thought that GERD produces extraesophageal symptoms through two main pathways: the "reflux theory," in which gastric contents are micro-aspirated into the upper airway, directly injuring the respiratory epithelium and activating inflammatory mediators; and the "reflex theory," in which reflux in the distal esophagus stimulates acid-sensitive receptors, triggering bronchoconstriction, cough, and airway hyperresponsiveness via a vago-vagal reflex arc. These mechanisms are not mutually exclusive and may act synergistically to produce extraesophageal symptoms [5,6].

Conventional esophageal pH monitoring detects only acid reflux and cannot identify non-acid or weakly acidic reflux. Multichannel intraluminal impedance-pH (MII-pH) monitoring builds on pH monitoring by additionally characterizing the composition of refluxate (liquid, gas, or mixed), the proximal extent of reflux within the esophagus, and reflux clearance time, and allows symptom–reflux association analysis (symptom association probability, SAP) [1]. Studies have shown that pH monitoring alone has a sensitivity of only 38.1% for detecting GERD in children with extraesophageal symptoms, compared with 63.8% in children with gastrointestinal symptoms; MII-pH can detect approximately 50% of GERD cases. Accordingly, the 2018 NASPGHAN/ESPGHAN joint guideline recommends MII-pH for correlating persistent symptoms with acidic and non-acidic reflux events, clarifying the role of reflux in esophagitis and other GERD-related symptoms, and evaluating the efficacy of acid-suppressive therapy [7–10].

In recent years, MII-pH technology has increasingly revealed the importance of non-acid reflux in extraesophageal symptoms. Earlier studies by Mattioli et al. [11] and Salvatore et al. [12] reached similar conclusions: among children older than 1 year, the proportion of non-acid reflux associated with respiratory symptoms was significantly higher than in the

gastrointestinal-symptom group (43% vs. 24%), although this difference was not apparent in infants. Furthermore, a systematic review by Chang et al. showed that a substantial proportion of patients with GERD-related respiratory symptoms did not improve with aggressive acid-suppressive therapy, further supporting the hypothesis that respiratory symptoms are less closely linked to reflux acidity than gastrointestinal symptoms [13]. More recent pediatric studies have extended these observations. Pavić et al. reported associations between acidic and weakly acidic reflux episodes and symptom and laryngoscopic scores in 113 children with suspected laryngopharyngeal reflux [14]. In a separate cohort of preschool children with severe recurrent wheeze, reflux characteristics were associated with bronchoalveolar lavage lipid-laden macrophages [15]. Galos et al. described age-dependent reflux patterns and an inverse association between mean nocturnal baseline impedance (MNBI) and acid exposure in 226 children [16].

Although the studies above provide important clues to understanding differences in reflux phenotype between children with extraesophageal and gastrointestinal symptoms, pediatric research in this field remains limited, and most existing studies have small sample sizes and lack control groups; differences in reflux characteristics across age groups have not been fully elucidated. Moreover, most prior studies originate from Europe and North America, and comparative studies of MII-pH reflux characteristics across different symptom presentations in Chinese children are lacking.

Therefore, this study aimed to use a single-center retrospective cross-sectional design and 24 h esophageal MII-pH monitoring to systematically compare children aged ≥1 year presenting predominantly with gastrointestinal symptoms, respiratory symptoms (chronic cough/wheezing), or chest symptoms (chest tightness/pain), in terms of reflux acidity distribution, reflux event frequency, and proximal extent of refluxate, with a separate exploratory comparison of infants with predominant gastrointestinal versus non-gastrointestinal symptoms.

2. Materials and Methods

2.1. Study Design and Ethical Approval

This was a single-center retrospective cross-sectional study. Children who underwent 24 h esophageal MII-pH monitoring in the gastrointestinal motility laboratory between September 2024 and June 2026 were retrospectively enrolled. The study protocol was approved by the institutional ethics committee (approval no. KY-2026-0327); given the retrospective design, informed consent was waived.

2.2. Instruments and Examination Methods

Esophageal multichannel intraluminal impedance-pH (MII-pH) monitoring was performed using a Laborie monitoring system. JSIpC catheters with an outer diameter of 2 mm, six impedance channels, and one pH electrode were used. Catheter configuration was selected according to age: a No. 54 catheter with an interelectrode spacing of 1.5 cm was used in infants aged <1 year, whereas a No. 57 catheter with an interelectrode spacing of 2 cm was used in children aged ≥1 year.

Before insertion, the pH electrode was calibrated using standard buffer solutions at pH 4.0 and 7.0. The catheter was inserted transnasally. In infants aged <1 year, the insertion depth to the pH electrode was estimated using the modified Strobel formula: insertion depth (cm) = [(body length in cm × 0.252) + 5] × 0.87. In children aged 1–7 years, the pH electrode was positioned 3 cm above the lower esophageal sphincter (LES); in children aged >7 years, it was positioned 5 cm above the LES. Esophageal manometry and/or the pH step-up method were used to determine or verify the position.

Parents or caregivers were instructed to maintain a monitoring diary documenting meal times and food consumed, the start and end times of supine periods, and the type,

onset, and end time of symptoms. The completeness of the 24 h recordings was checked before analysis. Recordings were initially analyzed using Laborie analysis software and subsequently reviewed and corrected manually by trained investigators to identify and remove artifacts. Feeding periods, body position, and symptom occurrences were annotated with reference to the monitoring diaries.

2.3. Study Subjects

Inclusion criteria: (1) age 0–18 years; (2) underwent 24 h esophageal MII-pH monitoring at our institution for suspected GERD-related symptoms (gastrointestinal, respiratory, chest, or other presenting symptoms); (3) proton pump inhibitors (PPIs) discontinued for at least 7 days and H2-receptor antagonists/prokinetic agents discontinued for at least 72 h before monitoring; (4) valid monitoring duration ≥18 h with acceptable data quality and a complete report; (5) a clearly identifiable primary or predominant presenting symptom.

Exclusion criteria: (1) prior esophageal or gastric surgery (including anti-reflux surgery); (2) a confirmed esophageal motility disorder (e.g., achalasia, systemic sclerosis); (3) severe neurological disease affecting esophageal motility; (4) use of acid-suppressive medication during monitoring; (5) incomplete MII-pH recordings or excessive artifact precluding analysis.

Grouping method: Patients were first divided into two age cohorts. Within the childhood cohort, the three groups were defined by the primary or predominant presenting symptom rather than by an established anatomical origin or reflux-related mechanism. The childhood cohort (≥1 year) was further divided into three subgroups: (1) gastrointestinal-symptom group—patients presenting primarily with typical gastrointestinal symptoms such as recurrent vomiting/regurgitation, heartburn, acid regurgitation, or dysphagia; (2) respiratory-symptom (chronic cough/wheezing) group—patients presenting primarily with chronic cough (>4 weeks) and/or recurrent wheezing, suspected to be GERD-related after respiratory evaluation excluded primary respiratory disease (e.g., asthma, airway foreign body, congenital airway malformation); (3) chest-symptom (chest tightness/pain) group—patients presenting primarily with recurrent chest tightness and/or non-cardiac chest pain, after cardiology evaluation excluded cardiac causes. The chest tightness/pain group was retained as a distinct clinical presentation because exclusion of a cardiac cause does not exclude an esophageal origin. The infant cohort (<1 year) was divided into a non-gastrointestinal-symptom group (including cyanosis, stridor, and cough/wheezing) and a gastrointestinal-symptom group. Children with overlapping gastrointestinal, respiratory, and/or chest symptoms were assigned to a single group according to the initial or predominant presenting complaint documented in the medical records. Group allocation therefore reflected the principal clinical presentation rather than the absence of symptoms from other categories. Grouping was performed independently by two investigators, with disagreements resolved by discussion to reach consensus. The case-selection flowchart is shown in Figure 1.

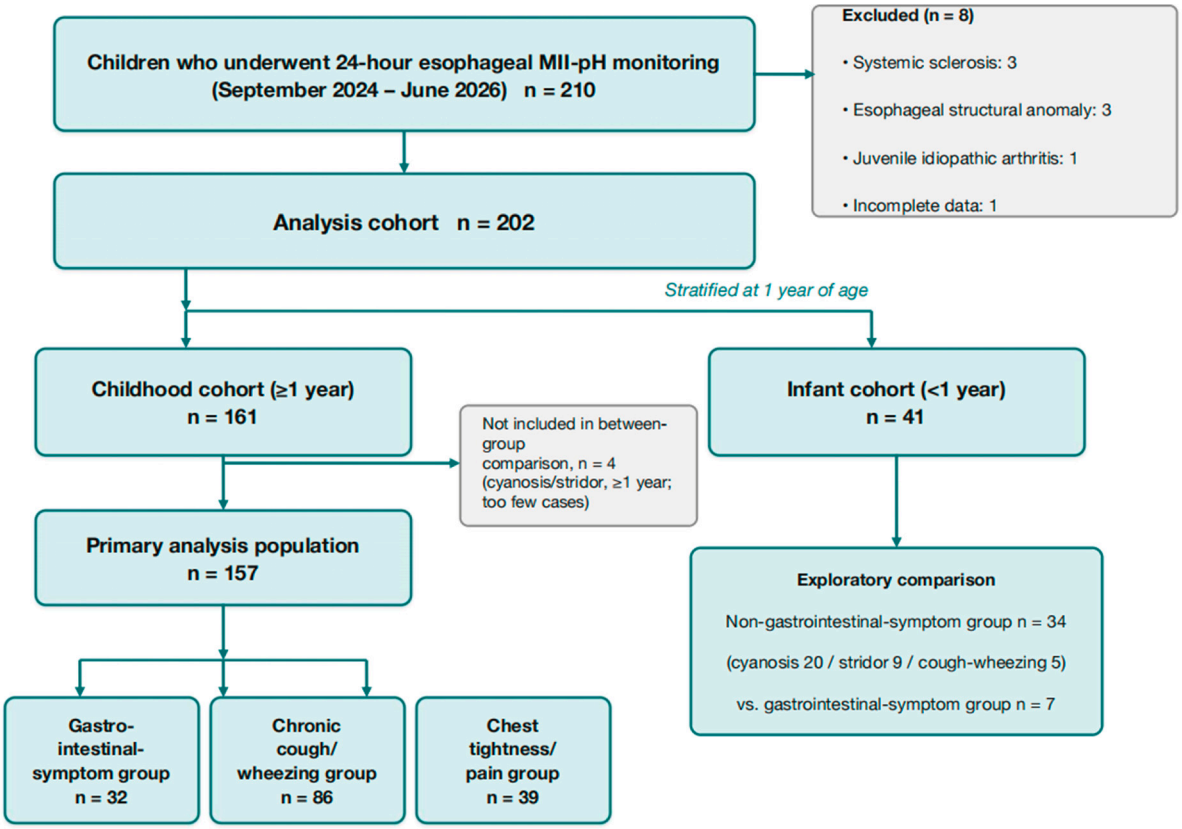

Figure 1. Flowchart of case selection.

2.4. MII-pH Data Analysis and Parameter Definitions

All MII-pH recordings were manually corrected by trained investigators on the basis of automated analysis, with meal periods marked.

Definition of a reflux event. A reflux event was defined as a retrograde fall in impedance of ≥50% from baseline in two consecutive distal impedance channels, lasting ≥4 s, in a liquid or liquid–gas mixed pattern. Based on the lowest pH recorded by the pH electrode during the reflux event, reflux events were classified as acidic reflux (pH < 4.0), weakly acidic reflux (pH 4.0–7.0), or weakly alkaline reflux (pH > 7.0).

Composition of refluxate. Based on the impedance change pattern, refluxate was classified as liquid reflux (retrograde impedance drop ≥ 50%), gas reflux (rapid impedance rise > 3000 Ω), or mixed liquid–gas reflux (liquid reflux accompanied by a gas component).

Proximal extent of reflux. The proximal extent of reflux was defined as the distance above the lower esophageal sphincter (LES) corresponding to the highest impedance channel reached by the reflux event.

pH-related parameters. The reflux index (RI) is the percentage of total monitoring time with esophageal pH <4.0. Abnormal thresholds: RI > 10% in infants (<1 year) and RI > 5% in children (≥1 year). Boix–Ochoa and DeMeester scores were extracted as recorded in the clinical reports and interpreted against their respective thresholds (Boix–Ochoa ≥ 11.99; DeMeester > 14.72). Values from the two scoring systems are not directly comparable across systems; each was interpreted against its own reference threshold in this study.

Impedance-related parameters. Total number of liquid reflux events and the number of events in each acidity category (acidic, weakly acidic, and weakly alkaline); weakly acidic reflux proportion (number of weakly acidic reflux events divided by total liquid reflux events, expressed as a percentage); number of proximal reflux events and proximal reflux ratio (number of proximal reflux events divided by total reflux events); reflux clearance

time; reflux exposure index (percentage of total monitoring time during which reflux was present in the esophagus).

Symptom–reflux association analysis. The symptom index (SI) is the number of symptom episodes associated with a reflux event divided by the total number of symptom episodes, ×100%; SI ≥ 50% was considered positive. The symptom association probability (SAP) uses Fisher's exact test to assess the temporal association between symptoms and reflux events; SAP ≥ 95% was considered positive. The time window for symptom–reflux association was defined as a reflux event occurring within 5 min before symptom onset. Although parents or caregivers were instructed to record symptoms during monitoring, sufficiently complete symptom-event records were unavailable in the retained retrospective data for reliable calculation or verification of the symptom index (SI), symptom association probability (SAP), or analyzable symptom-event counts by group.

Determination of the study conclusion. The report conclusions are interpreted by trained senior doctors based on the recorded Boix–Ochoa or DeMeester thresholds depending on age, acid exposure time, total number of liquid reflux events, and long reflux events. Monitoring and interpretation were performed as part of routine clinical care, and the clinicians had access to the patients' medical histories and presenting symptoms; therefore, blinding to presenting symptoms was not implemented. For this retrospective study, symptom groups were assigned subsequently on the basis of the primary or predominant presenting complaints documented in the electronic medical records.

2.5. Statistical Methods

Analyses were performed using SPSS 29.0. Continuous variables are expressed as median (P25, P75), and multi-group comparisons were performed using the Kruskal–Wallis test. The primary endpoint was the proportion of weakly acidic reflux events among total liquid reflux events in children aged ≥1 year. All other endpoints were considered secondary. Analyses of the infant cohort were considered exploratory. To adjust for between-group age imbalance, median (quantile) regression was used for continuous endpoints and logistic regression for the binary endpoint (abnormal report-based MII-pH classification), both adjusted for age and sex, with the gastrointestinal group as reference; β (95% CI) and OR (95% CI) are reported, respectively. Categorical variables are expressed as *n* (%) and compared using the χ^2 test or Fisher's exact test. Analyses used the available observations for each outcome separately. Missing data were handled by pairwise deletion. A two-sided $p < 0.05$ was considered statistically significant; secondary endpoints were not adjusted for multiple comparisons, and their results should be regarded as exploratory. The association between age and the weakly acidic reflux proportion was assessed using Spearman's rank correlation in the total cohort ($n = 202$). Locally weighted scatterplot smoothing (LOWESS) was used to visualize the relationship between age and the weakly acidic reflux proportion.

3. Results

3.1. General Characteristics

During the study period, 202 children meeting the eligibility criteria were enrolled: 115 boys (56.9%) and 87 girls (43.1%), with a median age of 7.28 years (P_{25}, P_{75}: 2.33, 10.56; range 0.02–17.20 years). The most common referring department was respiratory medicine (101 cases, 50.0%), followed by gastroenterology (45 cases, 22.3%), the NICU (25 cases, 12.4%), cardiology (19 cases, 9.4%), and the PICU (12 cases, 5.9%); referring department corresponded closely with the primary symptom: respiratory medicine was dominated by chronic cough/wheezing (77.2%), cardiology by chest tightness/pain (89.5%), gastroenterology by gastrointestinal symptoms (73.3%), and the NICU/PICU by cyanosis/stridor (Table S1). The recorded scoring system used was the Boix–Ochoa score in 126 patients (62.4%)

and the DeMeester score in 76 (37.6%); overall, 104 patients (51.5%) had an abnormal MII-pH classification recorded in the original clinical reports.

Stratifying at 1 year of age, the childhood cohort (≥1 year) comprised 161 patients and the infant cohort (<1 year) comprised 41 patients. The childhood cohort included the gastrointestinal-symptom group ($n = 32$), chronic cough/wheezing group ($n = 86$), and chest tightness/pain group ($n = 39$), totaling 157 patients; an additional 4 patients ≥1 year with cyanosis or stridor were excluded from between-group comparisons owing to their small numbers. The infant cohort comprised 20 cases of cyanosis, 9 of stridor, 5 of cough/wheezing, and 7 with gastrointestinal symptoms.

3.2. Comparison of Baseline Characteristics and MII-pH Parameters Among the Three Childhood Subgroups

3.2.1. Baseline Characteristics

There was no significant difference in sex distribution among the three groups (proportion male: 53.1%, 60.5%, and 53.8%, respectively; $p = 0.680$). The chest tightness/pain group was significantly older than the other two groups (median age 11.5 vs. 7.8 vs. 7.3 years, $p < 0.001$); this age difference was subsequently adjusted for using median (quantile) regression (Table 1).

Table 1. Baseline characteristics and MII-pH parameters among the three childhood subgroups.

Variable	Gastrointestinal Group ($n = 32$)	Chronic Cough/Wheezing Group ($n = 86$)	Chest Tightness/Pain Group ($n = 39$)	H/χ^2	*p*
Age, years	7.3 (3.7, 9.5)	7.8 (5.7, 10.6)	11.5 (8.8, 12.5)	23.17	<0.001
Male, *n* (%)	17 (53.1)	52 (60.5)	21 (53.8)	0.77	0.680
Scoring system, Boix–Ochoa/DeMeester, *n* *	21/11	53/33	10/29	16.34	<0.001
Acid exposure time, %	0.8 (0.3, 2.0)	0.6 (0.2, 1.1)	0.5 (0.2, 1.0)	2.75	0.253
Total liquid reflux events, *n*	41.0 (29.8, 60.5)	30.5 (19.5, 50.8)	32.0 (18.5, 44.0)	4.65	0.098
Weakly acidic reflux proportion, % **	57.2 (38.6, 75.8)	50.0 (36.4, 68.0)	51.6 (44.1, 59.5)	1.06	0.589
Acid reflux events, *n*	19.0 (6.8, 28.5)	13.0 (7.0, 21.0)	11.0 (7.0, 22.0)	1.26	0.531
Weakly acidic reflux events, *n*	23.5 (12.0, 36.2)	15.0 (7.2, 26.0)	16.0 (12.0, 23.0)	4.65	0.098
Weakly alkaline reflux events, *n*	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.79	0.675
Acid reflux reaching proximal esophagus, % ***	41.5 (24.8, 61.8)	43.0 (21.0, 60.0)	28.0 (13.0, 43.5)	7.03	0.030
Weakly acidic reflux reaching proximal esophagus, % ***	27.0 (19.0, 41.0)	28.0 (13.0, 38.0)	22.0 (14.0, 30.0)	1.89	0.388
Abnormal report-based MII-pH classification, *n* (%)	27 (84.4)	28 (32.6)	15 (38.5)	28.9	<0.001

Values are median (P_{25}, P_{75}) unless otherwise indicated. Kruskal–Wallis H test was used for continuous variables and the χ^2 test for categorical variables. * Boix–Ochoa or DeMeester score applied according to age, each interpreted against its own reference threshold. ** Primary endpoint. *** Acid and weakly acidic proximal reflux proportions each had 127 available observations; 110 children had both measures available. Each outcome was analyzed using its own available observations. The normal/abnormal classification was extracted from the original clinical MII-pH reports and did not represent an independently adjudicated diagnosis of GERD.

3.2.2. Weakly Acidic Reflux Proportion

The percentage of weakly acidic reflux events among total liquid reflux events did not differ significantly among the three groups. Median weakly acidic reflux proportions in the gastrointestinal, chronic cough/wheezing, and chest tightness/pain groups were 57.2% (IQR 38.6, 75.8), 50.0% (IQR 36.4, 68.0), and 51.6% (IQR 44.1, 59.5), respectively (Kruskal–Wallis $p = 0.589$) (Table 1). After adjustment for age and sex using median regression, the median difference (β) versus the gastrointestinal group was −6.01 (95% CI −18.02 to 6.00, $p = 0.325$) for the chronic cough/wheezing group and −8.30 (95% CI −22.95 to 6.35, $p = 0.265$) for the chest tightness/pain group, neither statistically significant (Table 2).

Table 2. Age- and sex-adjusted between-group differences in MII-pH parameters by median regression.

Endpoint	Chronic Cough/Wheezing vs. GI Group β (95% CI)	*p*	Chest Tightness/Pain vs. GI Group β (95% CI)	*p*
Weakly acidic reflux proportion, %	−6.01 (−18.02, 6.00)	0.325	−8.30 (−22.95, 6.35)	0.265
Acid exposure time, %	−0.23 (−0.60, 0.14)	0.220	−0.37 (−0.82, 0.08)	0.103
Total liquid reflux events, *n*	−8.00 (−18.81, 2.81)	0.146	−5.00 (−18.19, 8.19)	0.455
Acid reflux reaching proximal esophagus, %	0.87 (−15.28, 17.01)	0.916	−12.96 (−33.09, 7.16)	0.205
Weakly acidic reflux reaching proximal esophagus, %	0.20 (−10.48, 10.88)	0.971	−1.14 (−14.18, 11.91)	0.863

β = median difference relative to the gastrointestinal (GI) group, adjusted for age and sex. $n = 127$ for each proximal reflux outcome, using the available observations for that outcome separately; GI group as reference.

3.2.3. Reflux Severity Parameters

RI did not differ significantly among the three groups (0.8% vs. 0.6% vs. 0.5%, $p = 0.253$); after adjustment, the differences between each of the respiratory- and chest-symptom groups and the gastrointestinal group remained non-significant (chronic cough/wheezing group $\beta = -0.23$, $p = 0.220$; chest tightness/pain group $\beta = -0.37$, $p = 0.103$) (Tables 1 and 2). The total number of liquid reflux events did not differ significantly among the three groups (41.0 vs. 30.5 vs. 32.0, $p = 0.098$) and remained non-significant after adjustment (Tables 1 and 2).

3.2.4. Reflux Acidity Subtype Analysis

The number of acidic reflux events did not differ significantly among the three groups (19.0 vs. 13.0 vs. 11.0, $p = 0.531$). The number of weakly acidic reflux events showed a trend toward being higher in the gastrointestinal group (23.5 vs. 15.0 vs. 16.0, $p = 0.098$), which did not reach statistical significance (Table 1).

3.2.5. Proximal Reflux Ratio

Acid and weakly acidic proximal reflux proportions were each available for 127 of the 157 children; 110 children had both measures available. Missing acid proximal reflux proportions numbered 4/32, 17/86, and 9/39 in the gastrointestinal, respiratory, and chest symptom groups, respectively. The corresponding numbers for weakly acidic proximal reflux proportions were 7/32, 17/86, and 6/39.

In three children, the acid proximal reflux proportion was undefined because no acid reflux events were recorded, resulting in a zero denominator. The remaining 27 missing acid proportions and all 30 missing weakly acidic proportions had positive event-count denominators, but no usable proximal proportion was available in the retained records. The reasons could not be reliably distinguished among technical problems, unreported true zero values, incomplete reporting, and data transcription loss.

The proportion of acid reflux reaching the proximal esophagus differed significantly among the three groups (41.5% vs. 43.0% vs. 28.0%, Kruskal–Wallis $p = 0.030$) (Table 1). However, after adjustment for age and sex using median regression, the difference between the chronic cough/wheezing group and the gastrointestinal group disappeared ($\beta = 0.87$, 95% CI −15.28 to 17.01, $p = 0.916$), and the difference between the chest tightness/pain group and the gastrointestinal group also did not reach significance ($\beta = -12.96$, 95% CI −33.09 to 7.16, $p = 0.205$) (Table 2). The proportion of weakly acidic reflux reaching the proximal esophagus did not differ significantly among the three groups (27.0% vs. 28.0% vs. 22.0%, $p = 0.388$), and remained non-significant after adjustment (Tables 1 and 2). These findings indicate that children in the respiratory- and chest-symptom groups did not show a higher proximal reflux ratio.

3.2.6. Rate of an Abnormal Report-Based MII-pH Classification

The proportion of MII-pH studies classified as abnormal in the original clinical reports differed significantly among the three groups ($p < 0.001$). Abnormal report-based classifications were recorded in 84.4% (27/32) of the gastrointestinal group, significantly higher than 32.6% (28/86) of the chronic cough/wheezing group and 38.5% (15/39) of the chest tightness/pain group (Table 1).

Multivariable logistic regression (Table 3) showed that, with the gastrointestinal-symptom group as reference and after adjustment for age and sex, the odds of an abnormal report-based MII-pH classification were lower in the chronic cough/wheezing group (OR 0.064, 95% CI 0.021–0.200, $p < 0.001$) and the chest tightness/pain group (OR 0.093, 95% CI 0.026–0.329, $p < 0.001$). Age was not significantly associated with the classification outcome (OR 1.000, 95% CI 0.899–1.113, $p = 0.999$), whereas male sex was associated with higher odds of an abnormal report-based classification (OR 3.796, 95% CI 1.732–8.321, $p < 0.001$).

Table 3. Multivariable logistic regression for an abnormal report-based MII-pH classification (childhood cohort, $n = 157$).

Variable	OR (95% CI)	*p*
Symptom group (reference: gastrointestinal group)		
Chronic cough/wheezing group	0.064 (0.021, 0.200)	<0.001
Chest tightness/pain group	0.093 (0.026, 0.329)	<0.001
Age (per 1-year increase)	1.000 (0.899, 1.113)	0.999
Male (reference: female)	3.796 (1.732, 8.321)	<0.001

Dependent variable: original clinical report-based MII-pH classification (abnormal = 1). Adjusted for age and sex; reference group = gastrointestinal group.

3.3. Age-Related Distribution of the Weakly Acidic Reflux Proportion

Across all 202 patients, the weakly acidic reflux proportion was negatively correlated with age (Spearman $\rho = -0.214$, $p = 0.002$) (Figure 2). The LOWESS trend line showed that the weakly acidic reflux proportion was highest in infancy (approximately 74%), declined progressively to approximately 52% between 1 and 4 years of age, and then plateaued through adolescence at approximately 50–60%. This negative correlation was

driven primarily by infants younger than 1 year, providing further support for the 1-year stratification used in this study.

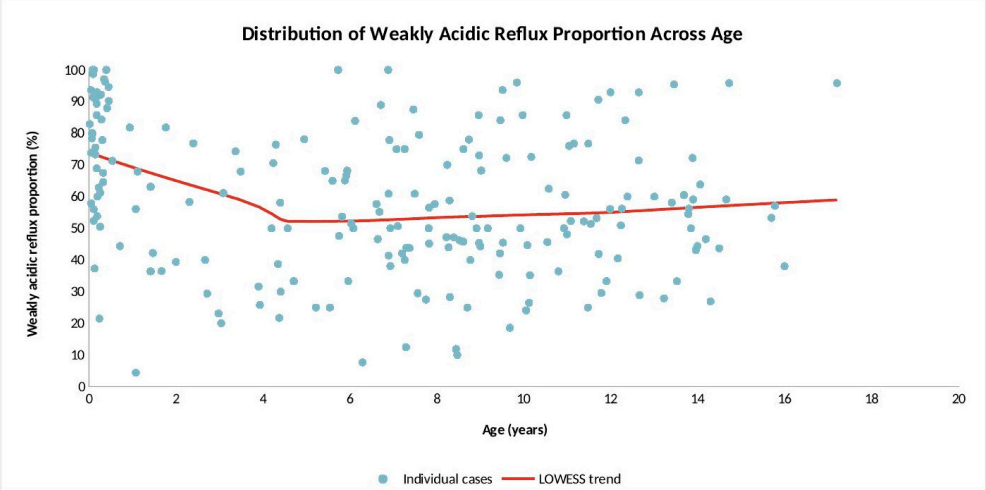

Figure 2. Distribution of the weakly acidic reflux proportion across age. Points represent the weakly acidic reflux proportion for individual cases; the red line is the locally weighted scatterplot smoothing (LOWESS) trend; the dashed line marks the 1-year cutoff. The weakly acidic reflux proportion was negatively correlated with age (Spearman $\rho = -0.214$, $p = 0.002$). An editable native chart (data + trend line) is provided in the Supplementary Materials.

3.4. Exploratory Comparison Within the Infant Cohort

The infant cohort comprised 41 patients: 34 in the non-gastrointestinal-symptom group (20 with cyanosis, 9 with stridor, 5 with cough/wheezing) and 7 in the gastrointestinal-symptom group. Age did not differ significantly between the two groups (median 0.2 years in both, $p = 0.488$) (Table 4).

Table 4. MII-pH parameters between the non-gastrointestinal-symptom and gastrointestinal-symptom subgroups in infants (exploratory).

Variable	Non-Gastrointestinal-Symptom Group ($n = 34$)	Gastrointestinal-Symptom Group ($n = 7$)	p
Age, years	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.488
Boix–Ochoa score *	6.6 (3.4, 14.4)	15.6 (12.0, 30.9)	0.023
Acid exposure time, %	1.8 (0.3, 3.4)	4.9 (2.7, 5.6)	0.054
Total liquid reflux events, *n*	49.5 (22.8, 76.5)	97.0 (86.0, 110.0)	0.004
Weakly acidic reflux proportion, %	83.6 (70.0, 92.7)	62.9 (48.4, 67.9)	0.008
Acid reflux events, *n*	7.5 (2.2, 11.0)	36.0 (29.5, 42.5)	<0.001
Weakly acidic reflux events, *n*	36.0 (15.0, 53.8)	61.0 (41.5, 83.0)	0.093
Acid reflux reaching proximal esophagus, %	45.0 (25.0, 50.0)	52.5 (46.0, 56.8)	0.399
Weakly acidic reflux reaching proximal esophagus, %	33.5 (24.8, 53.2)	38.0 (22.2, 53.0)	0.857
Abnormal report-based MII-pH classification, *n* (%)	25 (73.5)	7 (100.0)	—

Mann–Whitney U test. The non-gastrointestinal-symptom group includes 20 with cyanosis, 9 with stridor, and 5 with cough/wheezing. * Boix–Ochoa score used for the infant cohort.

The degree of reflux was significantly greater in the gastrointestinal-symptom group than in the non-gastrointestinal-symptom group. The total number of liquid reflux events

was 97.0 (IQR 86.0, 110.0) in the gastrointestinal group, significantly higher than 49.5 (IQR 22.8, 76.5) in the non-gastrointestinal group ($p = 0.004$). The number of acid reflux events was also significantly higher in the gastrointestinal group (36.0 vs. 7.5, $p < 0.001$). The Boix–Ochoa score was 15.6 (IQR 12.0, 30.9) in the gastrointestinal group, higher than 6.6 (IQR 3.4, 14.4) in the non-gastrointestinal group ($p = 0.023$). Acid exposure time trended higher in the gastrointestinal group (4.9% vs. 1.8%, $p = 0.054$) (Table 4).

In contrast to the childhood cohort, the weakly acidic reflux proportion was significantly higher in the non-gastrointestinal group than in the gastrointestinal group in infants (83.6%, IQR 70.0–92.7 vs. 62.9%, IQR 48.4–67.9, $p = 0.008$) (Table 4). The absolute number of weakly acidic reflux events did not differ significantly between the two groups (36.0 vs. 61.0, $p = 0.093$), suggesting that the higher weakly acidic reflux proportion in the non-gastrointestinal group may be driven mainly by a reduction in acid reflux events rather than an increase in weakly acidic reflux events.

There were no significant differences between the two groups in the proportion of acid reflux reaching the proximal esophagus (45.0% vs. 52.5%, $p = 0.399$) or the proportion of weakly acidic reflux reaching the proximal esophagus (33.5% vs. 38.0%, $p = 0.857$) (Table 4). The rate of an abnormal report-based MII-pH classification was 100.0% (7/7) in the gastrointestinal group and 73.5% (25/34) in the non-gastrointestinal group. Given that the gastrointestinal group comprised only 7 patients, these findings should be regarded as exploratory and require confirmation in future prospective studies.

4. Discussion

This retrospective cross-sectional analysis included 202 children. The principal comparison of 157 children aged ≥1 year evaluated reflux characteristics across gastrointestinal-, respiratory- (chronic cough/wheezing), and chest-symptom (chest tightness/pain) groups; infants were analyzed separately. The main findings were as follows: (1) the weakly acidic reflux proportion did not differ significantly between either the respiratory- or chest-symptom group and the gastrointestinal-symptom group; (2) the proportion of abnormal classifications in the original clinical MII-pH reports was lower in the respiratory and chest symptom groups than in the gastrointestinal group; (3) the proximal reflux ratio did not differ between the groups; (4) in the infant cohort, the weakly acidic reflux proportion was significantly higher in children without gastrointestinal symptoms than in those with gastrointestinal symptoms. These findings suggest that children presenting predominantly with respiratory or chest symptoms did not exhibit a distinct reflux phenotype characterized by increased weakly acidic or proximal reflux, whereas report-based abnormal classifications were less frequent than in children with gastrointestinal symptoms.

4.1. Weakly Acidic Reflux Proportion Across Presenting-Symptom Groups

Prior studies have proposed that extraesophageal symptoms may be more closely linked to non-acid reflux, which could explain the limited efficacy of acid-suppressive therapy for such symptoms. In a prospective controlled study, Zenzeri et al. [1] found that children older than 1 year with GERD and respiratory symptoms had significantly more weakly alkaline reflux events than those with gastrointestinal symptoms, along with significantly lower esophageal acid exposure time and fewer acidic/weakly acidic reflux episodes. Mattioli et al. [11] and Salvatore et al. [12] reported similar findings: among children older than 1 year, the proportion of non-acid reflux associated with respiratory symptoms was significantly higher than in the gastrointestinal-symptom group (43% vs. 24%).

However, the present study did not replicate these findings. The weakly acidic reflux proportion did not differ significantly among the three groups (57.2% vs. 50.0% vs. 51.6%,

$p = 0.589$), and this difference remained non-significant after adjustment for age and sex. This discrepancy may reflect several methodological differences. First, most prior studies enrolled children with confirmed GERD for subgroup comparison, whereas the present study enrolled patients undergoing MII-pH monitoring for various presenting symptoms without pre-selecting for GERD positivity, more closely approximating a real-world "pre-test" clinical population. Second, the between-group difference reported by Zenzeri et al. was concentrated in weakly alkaline reflux, whereas the primary endpoint of the present study was the weakly acidic reflux proportion. Third, sample size differed—the childhood cohort in this study ($n = 157$) was larger than in prior comparable studies, providing relatively greater statistical power.

Our findings are consistent with the general caution expressed by Vaezi et al. [10] regarding the uncertain relationship between extraesophageal symptoms and reflux findings. Although the proportions of abnormal report-based classifications in our respiratory- and chest-symptom groups were 32.6% and 38.5%, respectively, these estimates should not be directly equated with abnormality rates reported in studies using different patient populations or interpretation criteria.

4.2. Proximal Reflux Across Presenting-Symptom Groups

In theory, reflux reaching the proximal esophagus or even the laryngopharynx is a prerequisite for the development of extraesophageal symptoms, particularly under the microaspiration mechanism described by the "reflux theory." Accordingly, it has been hypothesized that children with extraesophageal symptoms should show a higher proximal reflux ratio [1].

The present findings do not support this hypothesis. Although the unadjusted proportion of acid reflux reaching the proximal esophagus differed significantly among the three groups ($p = 0.030$), this difference disappeared after adjustment for age and sex (chronic cough/wheezing group $\beta = 0.87$, $p = 0.916$; chest tightness/pain group $\beta = -12.96$, $p = 0.205$), suggesting that the unadjusted difference may have been confounded by age (the chest tightness/pain group was notably older). The proportion of weakly acidic reflux reaching the proximal esophagus also did not differ among the groups.

This finding is consistent with studies cited in the ACG guideline [17], one of which found that, regardless of symptom type, approximately half of reflux events reached the proximal esophagus, with extraesophageal symptoms not more frequently accompanied by proximal reflux than typical GERD symptoms. Vaezi et al. [10] note that the literature remains conflicting on whether patients with extraesophageal manifestations have more high (proximal) reflux events. Zhang et al. [18] found that, in adults with GERD, the number of proximal reflux events was significantly higher in the respiratory-symptom group than in the non-respiratory-symptom group, but that study enrolled only patients with confirmed GERD, unlike the unselected population in this study.

The clinical significance of proximal reflux remains unclear, and diagnostic criteria for proximal reflux are not standardized across studies. Future studies could incorporate a pharyngeal impedance probe or salivary pepsin testing to improve sensitivity for detecting laryngopharyngeal reflux.

4.3. Differences in Report-Based MII-pH Classifications Across Symptom Groups

An additional finding of this study was the marked difference in the proportion of abnormal MII-pH classifications recorded in the original clinical reports across the three symptom groups. The proportions were 84.4% in the gastrointestinal-symptom group, 32.6% in the chronic cough/wheezing group, and 38.5% in the chest tightness/pain group. After adjustment for age and sex, the odds of an abnormal report-based classification

remained lower in the respiratory-symptom group (OR 0.064, 95% CI 0.021–0.200) and the chest-symptom group (OR 0.093, 95% CI 0.026–0.329) than in the gastrointestinal-symptom group. However, this secondary outcome should be interpreted cautiously because the classifications were derived from routine clinical reports rather than standardized, blinded research assessments [19].

These findings are broadly consistent with recommendations emphasizing that extraesophageal symptoms should not automatically be attributed to GERD [6,17]. However, the populations and assessment criteria in previous studies differ from those of the present study, and their reported frequencies of abnormal reflux findings are not directly comparable with our report-based classification rates. Importantly, the inability to retrospectively reconstruct a uniform decision rule, together with the clinicians' awareness of presenting symptoms, may have contributed to the substantial between-group differences observed in our study. Therefore, these differences should not be interpreted as demonstrating corresponding differences in independently confirmed GERD prevalence. Monitoring off acid-suppressive medication reduced concerns about the influence of ongoing acid suppression on reflux acidity measurements but did not eliminate potential clinical interpretation bias.

Prolonged reflux episodes (>5 min) were recorded in 5 of the 15 abnormal studies in the chest-symptom group (33.3%). This finding is descriptive and exploratory and does not establish impaired esophageal motility or clearance, neither of which was directly assessed in this study.

4.4. Age-Specific Reflux Pattern in the Infant Cohort

Analysis of the infant cohort revealed a reflux pattern distinct from that of the childhood cohort: the weakly acidic reflux proportion was significantly higher in the non-gastrointestinal group than in the gastrointestinal group (83.6% vs. 62.9%, $p = 0.008$). However, this difference was driven mainly by a significant increase in acid reflux events in the gastrointestinal group (36.0 vs. 7.5, $p < 0.001$), rather than by an increase in weakly acidic reflux events in the non-gastrointestinal group (36.0 vs. 61.0, $p = 0.093$).

An overall high weakly acidic reflux proportion in infancy has been widely reported. Rosen [20] noted that most reflux events in infants have a pH >4, largely because frequent feeding maintains a high intragastric pH for prolonged periods, and refluxate is predominantly non-acidic milk or formula. López-Alonso et al. [21] found that in healthy preterm infants, approximately 73% of reflux events over 24 h were weakly acidic and only 25% were acidic, with weakly acidic reflux significantly increasing during feeding. A multicenter study by Cresi et al. [22] similarly found a positive correlation between age and the frequency of acid reflux events ($\rho = 0.37$)—that is, younger age was associated with fewer acid reflux events and a higher weakly acidic reflux proportion. The LOWESS trend line in Figure 2 of the present study visually illustrates this age-dependent pattern: the weakly acidic reflux proportion was highest in infancy (approximately 74%), declined to approximately 52% between 1 and 4 years, and then plateaued. Gan et al. [23] recently reported a similar age-stratified reflux pattern in children with airway malacia: children ≥1 year were predominantly acid reflux–dominant, while infants <1 year were predominantly weakly acidic reflux–dominant. Together, these findings suggest that the acidity distribution of reflux in infancy is strongly influenced by feeding pattern and gastric acid secretory maturity, a physiological background that should be fully considered when interpreting infant MII-pH results.

It should be emphasized that the infant gastrointestinal-symptom group comprised only 7 patients, limiting statistical power; these findings should be regarded as exploratory and require confirmation in prospective studies.

4.5. Implications for Clinical Practice

The findings of this study have the following implications for the clinical management of children presenting with respiratory or chest symptoms:

First, GERD should not be empirically presumed as the primary cause of respiratory or chest symptoms. Compared with the gastrointestinal-symptom group, the respiratory and chest-symptom groups had lower adjusted odds of an abnormal report-based MII-pH classification (OR 0.064, 95% CI 0.021–0.200, and OR 0.093, 95% CI 0.026–0.329, respectively). This is consistent with the recommendations of the CHEST guideline (2019) [13] and the NASPGHAN/ESPGHAN guideline (2018) [7]: empirical acid-suppressive therapy should not be used in children with chronic cough who lack gastrointestinal symptoms; acid-suppressive therapy should be considered only when typical GERD symptoms and/or diagnostic testing indicate GERD.

Second, the widespread empirical use of acid-suppressive therapy in children presenting with respiratory or chest symptoms is not supported. A randomized controlled trial of children with chronic cough found that lansoprazole did not significantly improve cough compared with placebo, and that serious adverse events (particularly lower respiratory tract infections) were significantly more frequent in the PPI group (OR = 6.56, 95% CI 1.18–26.25) [13].

Third, MII-pH monitoring provides objective measurements of reflux characteristics. However, this study did not assess diagnostic accuracy against an independent reference standard and therefore cannot establish negative predictive value in this population. A normal report-based monitoring classification should not be interpreted as excluding GERD or a reflux-related contribution to the presenting symptoms. For patients with a normal report-based classification, clinicians should actively pursue alternative diagnoses (e.g., airway hyperresponsiveness, upper airway cough syndrome, psychogenic chest pain) to avoid unnecessary prolonged acid suppression. For patients with an abnormal report-based classification, individualized anti-reflux therapy may be considered, guided by comprehensive assessment including symptom–reflux association analysis [6,24].

4.6. Limitations

This study has several limitations. First, the cross-sectional design cannot establish causality and can only describe differences in reflux characteristics between symptom groups. Furthermore, sufficiently complete symptom-event records were unavailable for reliable calculation or verification of SI and SAP. Although some clinical reports contained SAP descriptions, these could not be consistently linked to the presenting symptom defining each group and were not included as validated symptom-association outcomes. Unreported SI/SAP results were not treated as negative. Consequently, this study could not assess temporal symptom–reflux associations, and similarities or differences in reflux burden cannot establish or exclude an association between reflux events and the presenting symptoms. Second, as a single-center retrospective study, referral bias may exist—children with gastrointestinal symptoms more often presented to gastroenterology and may represent a subpopulation with more severe reflux, whereas children with respiratory or chest symptoms presented via respiratory medicine or cardiology and may include many patients with non-GERD etiologies. Third, grouping was based on the initial or predominant clinical presentation; some patients may have had overlapping gastrointestinal, respiratory, and/or chest symptoms, and the accuracy of grouping depends on the completeness of medical records. In addition, the clinicians interpreting the MII-pH recordings were aware of the patients' presenting symptoms, and a uniform decision rule for the final classification could not be reconstructed retrospectively. These factors may have contributed to differences in report-based classifications across symptom groups. Adjustment for age and sex does

not eliminate this potential interpretation bias, whose magnitude and direction cannot be determined from the available data. Fourth, the infant gastrointestinal-symptom group comprised only 7 patients, limiting statistical power, and related conclusions should be interpreted with caution. Fifth, the absence of an independent reference standard precludes assessment of diagnostic accuracy, including negative predictive value. In addition, the lack of treatment comparisons and follow-up data prevents conclusions about treatment effectiveness or the ability of MII-pH findings to predict treatment response. Sixth, pediatric MII-pH reference values are not yet fully standardized, and differences in threshold between scoring systems (Boix–Ochoa vs. DeMeester) may affect the determination of abnormal rates [7,12,13].

5. Conclusions

In children undergoing MII-pH monitoring off acid-suppressive medication, those presenting predominantly with respiratory symptoms (chronic cough/wheezing) or chest symptoms (chest tightness/pain) did not exhibit a distinct reflux phenotype characterized by increased weakly acidic or proximal reflux compared with children presenting with gastrointestinal symptoms. Although the proportions of abnormal classifications in the original clinical monitoring reports were lower in the respiratory- and chest-symptom groups, this secondary finding should be interpreted cautiously because of potential bias associated with non-standardized, symptom-aware clinical interpretation. These results do not establish or exclude a causal relationship between reflux and the presenting symptoms. Future prospective studies incorporating standardized and blinded interpretation, reliable symptom–reflux association analysis, and treatment follow-up are needed to clarify the clinical significance of MII-pH findings in children with different presenting symptoms.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children13111545/s1: Table S1: Cross-distribution of referring department and symptom group.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author, subject to institutional and ethical restrictions on the sharing of pediatric patient data.

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Abbreviations

The following abbreviations are used in this manuscript:

GERD	Gastroesophageal reflux disease
MII-pH	Multichannel intraluminal impedance-pH
RI	Reflux index
SI	Symptom index
SAP	Symptom association probability
LES	Lower esophageal sphincter
PPI	Proton pump inhibitor
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval

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