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ORIGINAL ARTICLE

Gastroenterology

The role of high-resolution impedance manometry to identify rumination syndrome in children with unexplained foregut symptoms

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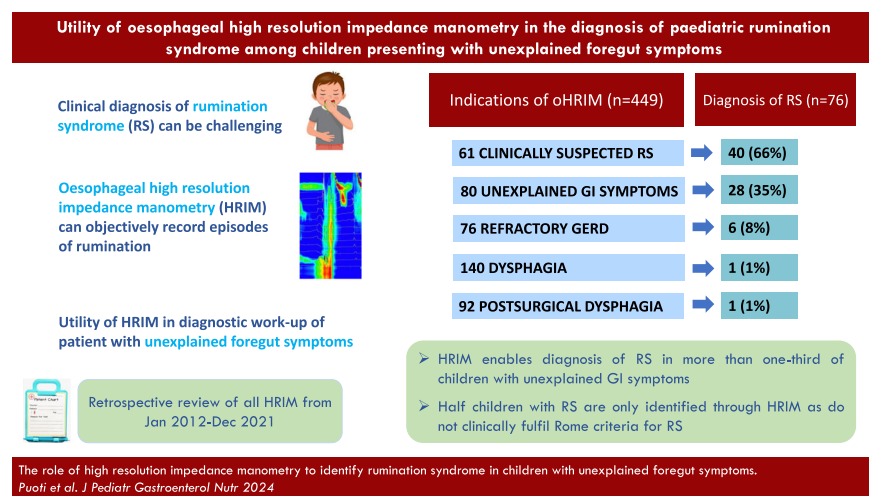Email: osvaldo.borrelli@gosh.nhs.uk

Abstract

Objectives: Diagnosis of rumination syndrome (RS) relies on Rome IV criteria. Oesophageal high-resolution impedance manometry (HRIM) can objectively demonstrate the episodes of rumination, but its role in the diagnostic pathway is not yet established. We aimed to demonstrate the clinical contribution of this tool for the timely diagnosis of RS and diagnostic work-up of children with unexplained foregut symptoms deemed to be due to other conditions.

Methods: HRIMs performed between 2012 and 2021 were searched to retrieve all diagnoses of RS. Medical records were reviewed for clinical data.

Results: Out of 461 HRIMs performed, 76 children had manometric diagnosis of RS (35 male, median age: 13 years). Of them, 47% were not clinically suspected as the symptoms did not fulfil clinical criteria for RS. The indications for HRIM in these cases were investigation of unexplained foregut symptoms (37%), suspected refractory gastroesophageal reflux disease (8%) and dysphagia (2%). Among all HRIMs performed for investigations of unexplained foregut symptoms ($n = 80$), 35% demonstrated rumination episodes.

Conclusion: Identification of characteristic patterns of rumination on HRIM in children with unexplained foregut symptoms enables the immediate diagnosis of RS. Thus, in situations of diagnostic uncertainty, the use of HRIM at early stages of the diagnostic pathway would reduce unnecessary investigations and treatments.

Utility of oesophageal high resolution impedance manometry in the diagnosis of paediatric rumination syndrome among children presenting with unexplained foregut symptoms

Clinical diagnosis of rumination syndrome (RS) can be challenging

Oesophageal high resolution impedance manometry (HRIM) can objectively record episodes of rumination

Utility of HRIM in diagnostic work-up of patient with unexplained foregut symptoms

Retrospective review of all HRIM from Jan 2012-Dec 2021

Indications of oHRIM (n=449)	Diagnosis of RS (n=76)
61 CLINICALLY SUSPECTED RS	40 (66%)
80 UNEXPLAINED GI SYMPTOMS	28 (35%)
76 REFRACTORY GERD	6 (8%)
140 DYSPHAGIA	1 (1%)
92 POSTSURGICAL DYSPHAGIA	1 (1%)

➤ HRIM enables diagnosis of RS in more than one-third of children with unexplained GI symptoms
➤ Half children with RS are only identified through HRIM as do not clinically fulfil Rome criteria for RS

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KEYWORDS

oesophageal high resolution manometry, paediatric, upper gastrointestinal symptoms

1 | INTRODUCTION

Rumination syndrome (RS) is a disorder of gut-brain interaction characterised by repetitive episodes of effortless regurgitation of gastric contents into the mouth, which are subsequently either rechewed and reswallowed or expelled.[1–6] These episodes occur soon after meals and are not preceded by retching.[1–6]

In clinical practice, children with RS present with a history of recurrent regurgitations or 'vomiting' following meals. The diagnosis is often delayed or missed due to lack of awareness among clinicians. Even with increased awareness, discriminating this disorder from other conditions may be challenging even for expert specialist physicians due to heterogeneity of symptom and overlap with other functional and nonfunctional gastrointestinal (GI) disorders, such as refractory gastroesophageal reflux disease (GERD) and gastroparesis.[7,8] This can result in diagnostic delay, excessive investigations, multiple ineffective treatments and possible consequences such as weight loss, malnutrition, electrolyte disturbances and impaired quality of life.[9–12] These factors might also lead to poor engagement with therapy, reduced patient and family trust and increased school absenteeism.[12]

Oesophageal high-resolution impedance manometry (HRIM) is currently advocated as the gold standard for confirming RS.[13,14] Rumination episodes can be objectively recorded as episodes of retrograde bolus movement associated with a rise of gastric pressure occurring either prior or during the retrograde bolus movement. Manometric subtypes of rumination have also been identified, which might affect choice of, and response to, therapy.[15–17]

What is Known

- Diagnosis of rumination syndrome (RS) is based on Rome IV criteria.
- Heterogeneity of symptomatology, overlap with other functional gastrointestinal disorders and symptom miscommunication make its diagnosis challenging.
- Despite high-resolution impedance manometry (HRIM) can detect rumination episodes, its role in diagnosing RS is not well established.

What is New

- HRIM enables diagnosis of RS in more than one-third of children with unexplained upper GI symptoms.
- Almost half of the patients diagnosed with RS on HRIM are not clinically identified as these cases do not fulfil Rome criteria for RS.
- HRIM can facilitate diagnosis of RS in children with unexplained foregut symptoms and avoid excessive investigations and treatments.

Despite the utility of HRIM, its place within the diagnostic pathway for RS is still not established and the diagnosis is currently based purely on clinical picture as per Rome III or IV criteria.

In the current study, we aimed to demonstrate the clinical contribution of HRIM for a timely diagnosis of RS as well as its utility in assessing children with

unexplained foregut symptoms deemed to be refractory and due to other conditions.

2 | MATERIALS AND METHODS

Clinical records of all patients who underwent HRIM during a 10-year period (January 2012 to December 2021) at our Institution were searched for clinical presentation, indications and manometric features for HRIM. Among patients with RS, further data on demographics, reasons and source for referral to our Institution, previous investigations and treatments were collected.

Indications for HRIM were classified as (1) Dysphagia; (2) Persistent symptoms of GERD; (3) Suspected RS; (4) Unexplained refractory foregut symptoms; (5) Ongoing dysphagia or upper GI symptoms after oesophageal surgery (i.e., antireflux surgery, Heller myotomy). Unexplained refractory foregut symptoms included recurrent vomiting or regurgitations, epigastric discomfort, nausea, retching/gagging, belching/burping and food refusal, which did not fit the clinical criteria for RS and were refractory to standard treatment such as acid suppression, antiemetics and prokinetics. Symptoms of refractory GERD were recurrent regurgitations or vomiting, heartburn, epigastric pain, hematemesis, acid taste in the mouth and respiratory symptoms, such as chronic cough, which were unresponsive to high-dose proton pump inhibitors (PPIs) therapy.

All children underwent HRIM using a solid-state manometric system (Solar GI HIRM system, Medical Measurement Systems) and a 10-F solid-state catheter (Unisensor AG) with 36 high-resolution pressure and either 12- or 16-impedance sensors. Intraluminal pressures recorded by internal pressure transducers were amplified, digitised and stored on a PC computer for analysis using commercially available software (Manometry and analysis software v8.21, Medical Measurement System).

Medications known to affect oesophageal motility and lower oesophageal sphincter (LOS) physiology such as baclofen, calcium-blocking agents and opioids, were discontinued in all children at least 72 h prior to the study. After a fasting period of at least 6 h, the catheter was placed trans-nasally into the stomach with a minimum of five pressure sensors located in the gastric lumen and the remaining pressure sensors spanning the entire length of the oesophagus allowing for simultaneous visualisation of both the upper oesophageal sphincter (UOS) and LOS. Recordings were performed in all patients in upright position. A standardised protocol was carried out, where baseline measurements of UOS and LOS pressures were followed by administering to the patients 10 swallows of 5 mL of liquid spaced apart by at least 30 s; a 200 mL drink taken by rapid, repeat swallows; and finally, if a major oesophageal motility disorder was not identified, a solid meal with postprandial observation from 30 min up to 2 h.

Impedance tracings were analysed for the occurrence of reflux episodes according to previously published criteria.[17] Briefly, reflux was defined by impedance as liquid, gas and mixed (combined liquid and gas). Liquid reflux was defined as a retrograde 50% fall in impedance on at least the two more distal impedance channels. Gas reflux was defined as a rapid increase in impedance >3000 ohms, occurring in any two consecutive impedance channels.[17] Rumination episodes were defined according to previously published criteria.[13,17,18] In brief, a rumination event on HRIM was defined as a rise in intragastric pressure (R-wave) of at least 25 mmHg associated with retrograde movement of gastric content, without retching, to the proximal oesophagus up to 10 s after the strain event followed by primary or secondary oesophageal peristalsis (Supporting Information: Figure S1).

All HRIMs were reviewed by at least two clinicians independently. Where different conclusions were reported, a third clinician was involved and agreement was reached.

Descriptive analysis was used to evaluate the baseline characteristics of the patients. Continuous variables were reported as median and interquartile range (IQR) (25th–75th IQR). Continuous variables were consequently compared using Mann-Whitney U test. Categorical variables were presented as percentages and compared by using χ^2 test or Fisher exact test, as appropriate. All statistical tests were 2-tailed using 0.05 level of significance. Analysis was performed using Prism software version 8.00 (GraphPad).

The Research and Development Office of Great Ormond Street Hospital approved the review of the HRIM and clinical records for the research proposed in this study (R&D: 3364).

3 | RESULTS

Four hundred sixty-one HRIMs were performed in 427 children (male 45%; median age 11 years, IQR 6–14) over the study period. Indications for HRIM were dysphagia (30%), postsurgical dysphagia (20%), unexplained refractory foregut symptoms (17%), refractory GERD (16%) and clinical suspicion of RS (14%). No data were available in 12 cases (3%). In 76 children (35 male, median age 13 years, 11–14.25 IQR) HRIM pattern was consistent with RS. Median age at onset of symptoms was 10.2 years (IQR 8–13.2), while the median time from symptom onset to diagnosis was 21 months (IQR 7–37.5).

HRIM confirmed the diagnosis of RS in two-third of children (66%) in whom the diagnosis was previously clinically suspected ($n = 61$). It also enabled the identification of RS as the underlying diagnosis in
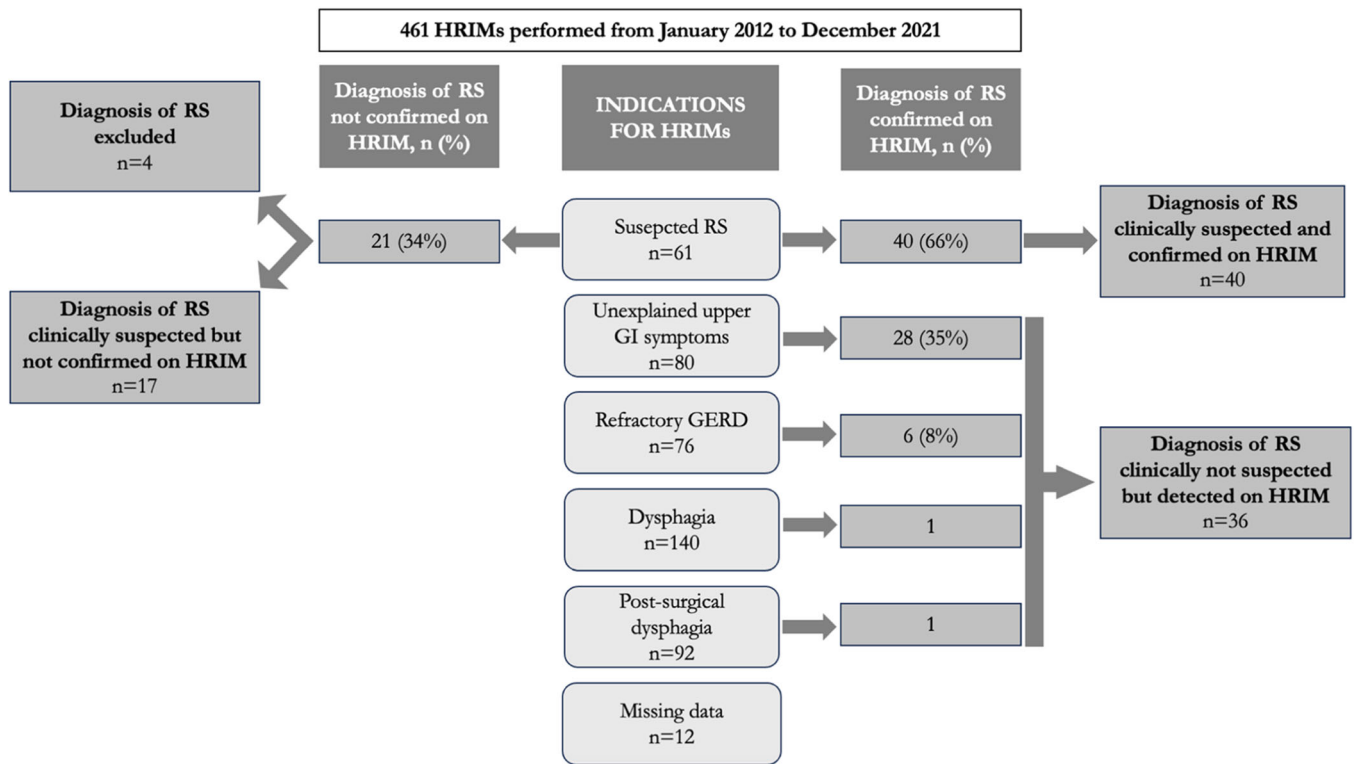
FIGURE 1 Indications and results of all oesophageal high-resolution impedance manometries (HRIMs).

35% of cases presenting with unexplained foregut symptoms ($n = 80$), 8% cases with refractory GERD ($n = 76$) and in two cases of dysphagia (Figure 1). Hence, in almost half of children (47%) with a final diagnosis of RS ($n = 76$) the diagnosis was not suspected purely on clinical picture, as symptoms did not completely fulfil either Rome IV criteria for RS. Table 1 summarises which criteria for RS were not met.

Among the patients suspected clinically to have RS ($n = 61$), one-third had a negative HRIM with no rumination event recorded. Then HRIM failed to confirm diagnosis of RS in 34%. Of them, 81% (five male, median age 10 years, 9–14 IQR) were given a diagnosis of RS based on Rome IV criteria. The remaining children (19%) received diagnosis of GERD ($n = 2$) and eosinophilic esophagitis ($n = 2$) with complete symptom response to appropriate treatment (Figure 1).

3.1 | Reason and source of referral of children diagnosed with RS on HRIM

Among all children diagnosed with RS on HRIM ($n = 76$) the reasons for referral to our centre were refractory GERD (28%), unknown organic cause of vomiting (26%), gastroparesis (12%), cyclical vomiting syndrome (8%), suspected oesophageal dysmotility (4%), food allergy (4%), eosinophil esophagitis (3%) and eating disorder (1%). The clinical question of

TABLE 1 Summary of criteria for diagnosis of RS not fulfilled in 36 cases among 76 patients diagnosed with RS on HRIM.

Criteria	No (%)
Regurgitation not only related to meal	19 (53%)
Regurgitation of both solid and liquid content	9 (25%)
Regurgitation occurring overnight	6 (17%)
Retching	3 (8%)
Regurgitation only of liquid content	1 (3%)

Abbreviations: HRIM, high-resolution impedance manometry; RS, ruminations syndrome.

possible RS was only found in 14% of referrals ($n = 11$). After assessment at our Institution, a clinical suspicion of RS was raised in 29 more patients resulting in a total of 40 children where clinical susoicion of RS was confirmed on HRIMs (Figure 1).

The referring clinicians were paediatric gastroenterologists (54%), general paediatricians (39%) and paediatric surgeons (7%).

3.2 | Clinical features of children diagnosed with RS on HRIM

Among patients diagnosed with RS on HRIM ($n = 76$), the most common GI symptom at presentation was

effortless regurgitation (75%), while vomiting was reported in the remaining (24%). In one patient, neither vomit nor regurgitation was reported but only acid reflux. Reswallowing of regurgitated food was only described by 24% of children. Others digestive symptoms, rather than the key clinical features of RS (regurgitation, reswallowing and spitting out), were reported at presentation in 76% of children: abdominal pain (51%), constipation (30%), nausea (21%), reflux-like symptoms (25%), belching (18%), heartburn (14%), bloating (9%), retching (7%) and diarrhoea (4%). Weight loss was reported in 35%.

Table 2 shows a comparison of clinical characteristics between children presenting with symptoms clearly suggestive of RS and meeting Rome criteria for RS and ones were not.

Moreover, 20% had psychological or psychiatric disorders and 5% neurodisability.

Nine children had comorbidities: eosinophilic esophagitis (n = 4), eosinophilic GI disease (n = 1), myasthenia gravis, (n = 1) diabetes type I, (n = 1), autoimmune hepatitis (n = 1) and bone marrow transplant for refractory acute myeloid leukaemia (n = 1).

3.3 | Investigations undergone before diagnosis in children diagnosed with RS on HRIM

An extensive work-up was performed for most of the children with all but one having performed at least one investigation before the referral (Figure 2). A median number of 5 (IQR 3–6) investigations were performed, with a maximum of 10 investigations for a single patient.

TABLE 2 Clinical characteristics of children that fulfil or not Rome III or IV criteria for RS.

Variables	Clinically suspected (n = 40)	Clinically not suspected (n = 36)	p Value
Age, median in years (IQR)	14.3 (5.4–18)	12.5 (7.6–16.1)	0.02
Male sex, no (%)	18 (45%)	15 (42%)	0.8
Time to diagnosis, median months (IQR)	16.5 (1–118)	25 (3–146)	0.2
Requirement of enteral feeding, no (%)	4 (10%)	16 (44%)	0.001*
Regurgitation, no (%)	32 (80%)	25 (69%)	0.28
Reswallowing, no (%)	15 (38%)	3 (8%)	0.003*
Reflux-like symptoms, no (%)	6 (15%)	13 (36%)	0.03*
Heartburn, no (%)	5 (13%)	6 (17%)	0.61
Dysphagia, no (%)	1 (3%)	5 (14%)	0.07
Nausea, no (%)	5 (13%)	12 (30%)	0.02*
Vomiting, no (%)	23 (58%)	22 (61%)	0.75
Retching, no (%)	0	5 (14%)	NA
Abdominal pain, no (%)	18 (45%)	21 (58%)	0.35
Belching/burping, no (%)	3 (8%)	11 (31%)	0.009*
Bloating, no (%)	1 (3%)	6 (17%)	0.03*
Constipation, no (%)	9 (23%)	14 (39%)	0.12
Weight loss, no (%)	9 (23%)	18 (50%)	0.01*
Fatigue, no (%)	7 (18%)	16 (44%)	0.01*
Headache, no (%)	6 (15%)	14 (39%)	0.02*
Joint pain, no (%)	3 (8%)	6 (17%)	0.2
Postural dizziness, no (%)	2 (5%)	6 (17%)	0.09
Sleep disturbances, no (%)	2 (5%)	6 (15%)	0.09

Abbreviations: IQR, interquartile range; RS, rumination syndrome.

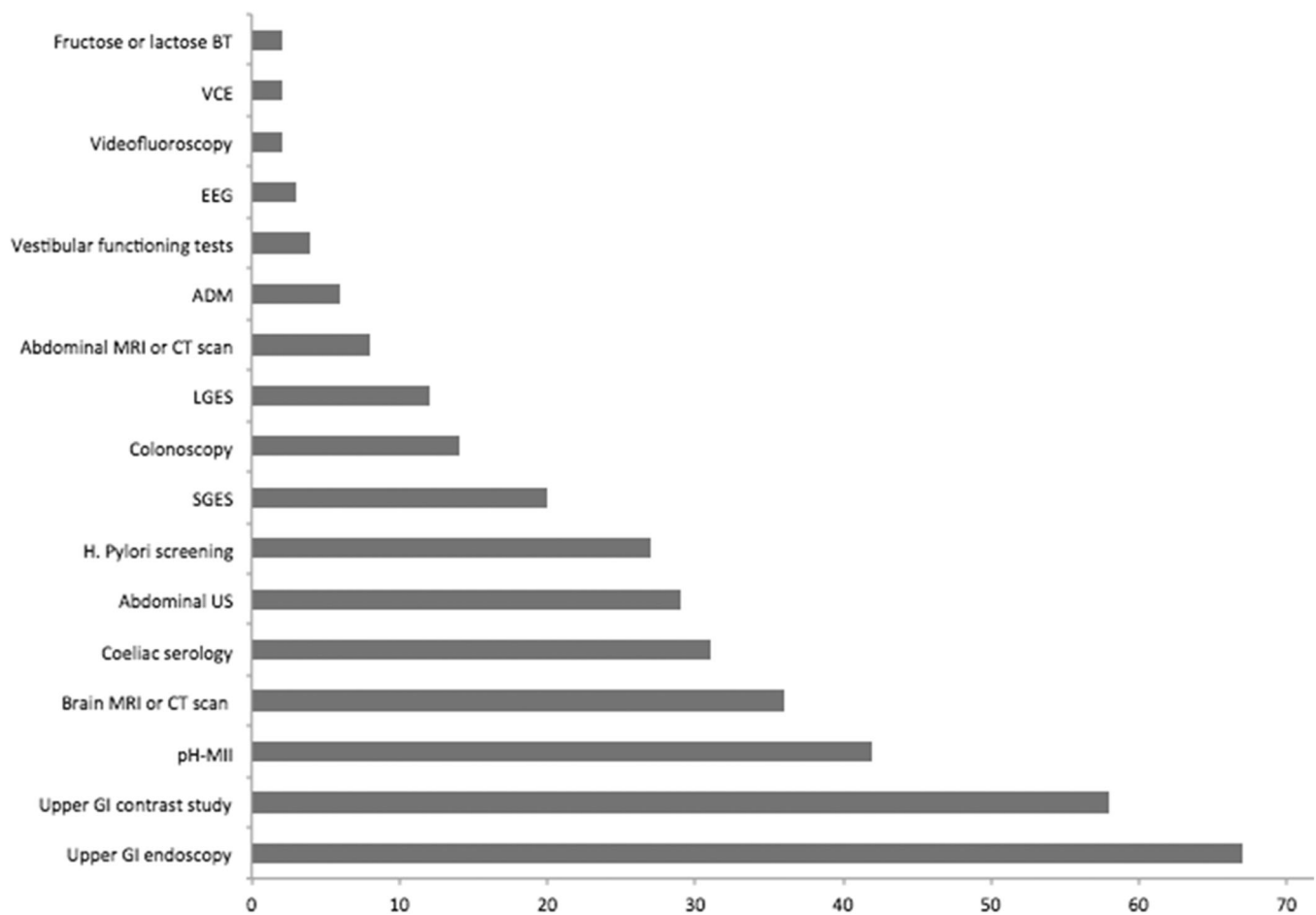*p value statistically significant as <0.05.

FIGURE 2 Investigations performed in our cohort of children diagnosed with ruminations syndrome (RS) on high-resolution impedance manometry (HRIM) during the diagnostic work-up. ADM, antroduodenal manometry; BT, breath test; CT, computerised tomography; EEG, elettroencephalography; GI, gastrointestinal; LGES, liquid gastric emptying scintigraphy; MRI, magnetic resonance imaging; pH-MII, multichannel intraluminal impedance and pH monitoring; SGES, solid gastric emptying scintigraphy; US, ultrasound; VCE, video capsule endoscopy.

Fourty-seven percent of patients had one or more spurious or borderline abnormalities on previous tests, which were either normal on repeat testing or with no clinical significance or had another condition diagnosed during the workup (Table S1).

3.4 | Treatment before the diagnosis in children diagnosed with RS on HRIM

Ninety-six percent of patients were tried on at least one treatment before assessment in our Institution (Table S2). A median number of 2 (IQR 1–3.25) medications per patient was prescribed for management of symptoms prior the referral. The highest number of medications prescribed for a single patient before referral was 9.

Nutritional and surgical treatments were also attempted before referral. Enteral feeding was required in 26%, via either nasogastric tube in 75%

and/or via nasojejunal tube in 30% of them. One patient received a course of parenteral nutrition due to inability to tolerate enteral feeding. Thirty-four percent of patients were tried on exclusion diets including exclusion of one or more of the following foods: gluten, cow's milk protein, eggs and soya. Elemental diet was tried in one case. Endoscopic and surgical treatments were performed in 5%: Nissen fundoplication ($n = 2$), endoscopic dilation of LOS ($n = 1$) and insertion of endoscopic percutaneous gastro-jejunostomy ($n = 1$).

4 | DISCUSSION

Our study demonstrated that HRIM was an essential diagnostic tool to establish the right diagnosis in half of children diagnosed with RS. This subgroup clinically did not fulfil clinical criteria for RS and most of them (two-third) presented with unexplained upper GI symptoms.

A notable finding was the significant prevalence (67%) of digestive symptoms other than the characteristic clinical features of RS (regurgitation, rechewing and spitting out) highlighting, not only that RS can encompass a much broader presentation than traditionally accepted, but suggests that the criteria for its suspicion and diagnosis needs to be reassessed. This result is consistent with other studies that have shown a higher number of patients with RS reporting symptoms overlapping with GERD and functional dyspepsia, such as postprandial discomfort, nausea and early satiety.[3,9,12] Chial et al. previously described a large cohort of children with RS who also presented with a number of associated symptoms, including abdominal pain, which was the most common.[12] In our study, reswallowing was reported only in 24% of patients. Previous studies reported a broad spectrum of these symptoms with reswallowing ranging from 17% up to 74%, spitting out up to 26% and rechewing in 3%.[3,13] These disparities may be because of different size sample between studies or inability of children and their caregivers to describe accurately the symptoms.

Interestingly, the subgroup of children diagnosed with RS by HRIM who did not fulfil clinical criteria showed higher prevalence of GI and extra-GI symptoms and significantly less reported reswallowing. This subgroup also required more often enteral feeding probably reflecting a longer time from onset of symptoms to diagnosis even if not statistically significant. Whether these symptoms reflect a coexistence with other DBGI, such as dyspepsia, or a broadened expression of the clinical picture of RS needs to be further elucidated. This raises the possibility that RS may represent an umbrella diagnosis with a number of subtypes related to different aetiopathogeneses or pathophysiologies.

Reason for referral were very varied, with only 14% referred with a suspicion of RS, highlighting the need for increased clinical suspicion of RS as a possible diagnosis in children presenting with effortless regurgitation. Tucker et al. similarly reported that 70% of adults diagnosed with RS by HRIM had been referred for unexplained chronic repetitive vomiting and only 17% of referral letters included RS in the differential diagnosis.[19] In our cohort, 28% of children diagnosed with RS by HRIM were labelled as refractory GERD by referring clinicians and referred for consideration of antireflux surgery, raising concern for unnecessary surgery if HRIM had not been performed.

Moreover, one of the most common reasons for referral was 'vomiting' (26%), highlighting that for most patients and families, this term is the only accurate description of the symptoms available to them. This raises the issue that miscommunication about clinical picture is one of the contributing factors for the delayed or missed diagnosis. Direct questions about effortless regurgitations during collection of clinical history may improve detection of this condition. Noteworthy, half of the patients were referred from paediatric gastroenterologists highlighting the significant challenges posed to diagnose RS based exclusively on clinical criteria even for specialists. Multiple factors can make the clinical diagnosis of RS very challenging and mislead clinician from the exact diagnosis such as associated GI and extra-GI symptoms, miscommunication of symptoms from patients/families, presence of comorbidities and coexistence with other functional and nonfunctional GI disorders.[3]

As reported in other studies, we identified that an extensive work-up had been performed in most of the children.[12,20] The extensive work-up led to a focus on spurious or borderline abnormalities of no clinical relevance in half of the children, which likely have represented one of the factors contributing to a delayed diagnosis. These confounding results often further entrench the medicalization of symptoms in the minds of both patients and families and might drive to an endless desire to seek further an organic diagnosis.

In our study, multiple treatments were unsuccessfully tried in almost all children prior the diagnosis. PPIs were tried in 87%, implying that GERD was initially suspected in the vast majority of cases. Noteworthy, 25% required enteral feeding and 5% received inappropriate surgical treatment before referral.

Despite the utility of HRIM in observing and subtyping rumination episodes, two drawbacks should be taken into consideration. First HRIM can fail to confirm diagnosis of RS as the rumination events may not occur during the recording. In our study, this was the case in one-fourth of children with suspected RS based on clinical presentation. Therefore, clinical diagnosis has still a key role to make the diagnosis of RS in children presenting with typical clinical picture and fulfilling clinical criteria for RS. Second, the use of HRIM is not widespread, it is difficult to perform in paediatric population and requires high level of expertise, which is limited to few paediatric gastroenterology centres.

However, our results demonstrated that in half of children diagnosed with RS clinical presentation was not clearly suggestive of this disorder, and only the performance of HRIM enabled the diagnosis of RS. Of note, among these patients 77% presented with unexplained foregut symptoms (Figure 1).

Based on our result, HRIM should be considered as supporting tool in selected cases. It would be worth considering whether HRIM should also be one of the first diagnostic tools to assess children presenting with unexplained foregut symptoms, as it would in our opinion, avoid multiple investigations and unnecessary treatments and possibly gain improved engagement with treatment of patients and their families.

In resource-limited centre where HRIM is not available, video recording the symptoms may be helpful to observe and differentiate between belching, retching, regurgitation and vomiting, to support clinical diagnosis of RS. Moreover, it has been recently suggested 24-h pH-impedance test could support physicians in achieving an early diagnosis of RS by using a specific and sensitive scoring system.[21]

It is also important to point out that enhanced diagnostic confidence performed in a timely fashion could limit the significant utilisation of healthcare resources. The average cost burden of diagnostic workup per child diagnosed with RS has already been estimated to be around US $ 20,000.[20]

This study has some limitations. First, this is a retrospective assessment of data collected prospectively for our database of HRIMs. Embracing the well-known limitations of this type of methodology, such as reliance on both referral letter and child/parental recall and potential incomplete data, we acknowledge the effects of these on our data. However, to minimise these limitations and increase the reliability of our data, we created a priori a structured form for data extraction as well as using an interobserver assessment for conflicting data. A well-designed prospective study would have been the most appropriate approach but we are reporting data over a span of 10 years. Second, the study was conducted in a quaternary referral centre with the potential bias of including a larger number of complex cases. However, this reflects the need for expertise and access to manometric assessment for diagnosis of RS in a significant number of cases. Finally, the sample size and potential skewing of the data might be the source of a type II error. However, the use of an objective assessment for the diagnosis of rumination would seem to benefit the strength of the results and our sample size seems large enough to provide clinically relevant information.

In conclusion, about half of the children with RS have a heterogeneous clinical presentation, which does not satisfy Rome clinical criteria. This heterogeneity significantly delays the diagnosis and leads to multiple misleading investigations and potential inconsistent management, which could be avoided with an early use of HRIM. Hence, we would suggest an established role of HRIM in the diagnostic pathway of RS as well as reconsideration of its role in the assessment of children with unexplained foregut symptoms.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

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