

# Patient journey in gastroesophageal reflux disease: real-world perspectives from Italian gastroenterologists, primary care physicians, and ENT specialists

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## Abstract

**Background:** Gastroesophageal reflux disease (GERD) is a challenging condition that involves different physicians, such as general practitioners (GPs), gastroenterologists, and ears, nose and throat (ENT) specialists. A common approach consists of proton-pump inhibitors (PPIs) administration. Adjunctive pharmacological treatment may have a role in the management of non-responders to PPIs.

**Objectives:** We aimed to survey GPs and different medical specialists to investigate the medical approaches to patients reporting GERD symptoms. In addition, we examined the use of adjunctive pharmacological treatments in patients with GERD symptoms who do not respond to PPIs.

**Design:** Retrospective observational study.

**Methods:** A survey was conducted among a large sample of gastroenterologists, GPs, and ENT specialists. Symptoms were divided into typical and extraesophageal, and their severity and impact on quality of life were explored with the GERD Impact Scale and with Reflux Symptom Index (RSI). All therapies administered usually for GERD were investigated.

**Results:** A total of 6211 patients were analyzed in this survey. Patients with typical symptoms were 53.5%, while those with extraesophageal symptoms were 46.5%. The latter were more frequently reported by ENT patients (53.6%,  $p < 0.0001$ ). The GSI was higher in patients followed by gastroenterologists (9 points) and GPs (9 points) than ENT specialists (8 points), but the RSI was higher in the ENT group ( $14.3 \pm 6.93$ ) than in GPs and gastroenterologist groups ( $10.36 \pm 6.36$  and  $10.81 \pm 7.30$ ,  $p < 0.0001$ ). Chest pain had the highest negative impact on quality of life ( $p < 0.0001$ ). Of the 3025 patients who used PPIs, non-responders showed a lower GSI when treated with a combination of adjunctive pharmacological treatments and bioadhesive compounds, than with single-component drugs.

**Conclusion:** Patients with GERD referred to a gastroenterologist had more severe disease and poorer quality of life. The combination of adjunctive pharmacological treatments and bioadhesive compounds seems to be effective in the management of PPI refractory patients.

## Plain language summary

### Gastroesophageal reflux disease management: real-world perspectives from Italian gastroenterologists, primary care physicians and ENT specialists

Gastroesophageal reflux disease (GERD) is a prevalent and chronic condition that affects millions of individuals worldwide, causing significant discomfort and impacting their

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overall quality of life. In the comprehensive management of GERD, a collaborative approach involving different physicians is essential to address the various aspects of this complex condition. Given the wide range of diagnostic and therapeutic possibilities in clinical practice, we aimed to investigate how GERD is managed in clinical practice by general practitioners and different medical specialists, including gastroenterologists and ears, nose, and throat (ENT) specialists. A total of 6,211 observations were carried out from a survey. The severity and impact of GERD on quality-of-life was higher in patients followed by gastroenterologists and general practitioners than ENT specialists. Non-cardiac chest pain had the highest negative impact on quality-of-life. Of the 3,025 patients who used PPIs, non-responders showed an improved quality of life when treated with a combination of adjunctive pharmacological treatments and bio adhesive compounds.

**Keywords:** GERD, reflux disease, acid suppressive therapy, mucosal protectants, alginate, atypical symptoms

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### Introduction

Gastroesophageal reflux disease (GERD) is a prevalent and chronic condition that affects millions of individuals worldwide, causing significant discomfort and impacting their overall quality of life.<sup>1</sup> GERD manifests through a wide range of symptoms that can be categorized as either typical (i.e. heartburn and regurgitation) or extraesophageal, which include asthma, chronic cough, laryngitis, hoarseness, persistent sore throat, dental erosions, and non-cardiac chest pain.<sup>2-4</sup> In Western countries, GERD is notably common, with an estimated prevalence between 10% and 30%.<sup>5</sup> The serious complications of GERD, such as erosive esophagitis, Barrett's esophagus, and esophageal cancer, underline the importance of the correct management of the disease.<sup>6</sup>

General practitioners (GPs), as frontline health-care providers, play a pivotal role in the diagnosis, management, and treatment of GERD patients.<sup>7</sup> At the same time, the role of other specialists is important for the management of challenging cases. Thus, in the comprehensive management of GERD, a collaborative approach involving different physicians is essential to address the various aspects of this complex condition.<sup>8</sup> Gastroenterologists play a crucial role in conducting diagnostic tests like endoscopy and pH monitoring to confirm GERD, and they offer expertise in prescribing medications and recommending lifestyle changes to alleviate symptoms.<sup>9</sup> Ear-nose-throat (ENT) specialists come into play

when GERD manifests with laryngopharyngeal reflux (LPR) or throat-related symptoms. They are trained in evaluating and managing the impact of GERD on the upper respiratory and digestive tracts, providing valuable insights into the holistic treatment of GERD.<sup>10</sup> Medical practitioners, including GPs and family physicians, also have an important role in GERD management. They provide the first contact point for many patients, offering early diagnosis, administering conservative treatment, and coordinating referrals to specialists when necessary.<sup>11</sup>

This intricate orchestra is essential for tailoring the most effective treatment to the patient based on their specific characteristics. In fact, the traditional treatments for GERD, such as proton-pump inhibitors (PPIs) and lifestyle modifications, have offered relief to many patients.<sup>9,12,13</sup> However, a substantial proportion of GERD patients, between 20% and 40%, continue to experience symptoms despite medical treatment.<sup>14-17</sup> Non-pharmacological approaches, including weight management, avoiding trigger foods, and moderate alcohol and smoking consumption, can play a complementary role in managing PPI-refractory GERD symptoms.<sup>13,18</sup> On the other hand, several adjunctive pharmacological treatments have been suggested in PPI-non-responder patients.<sup>19</sup> First, acid neutralizers can help to balance and reduce stomach acidity, alleviating epigastric discomfort and related symptoms.<sup>20</sup> Then, alginate-based compounds, working by neutralizing the gastric

acid pocket and by filming the esophageal mucosal surface, can prevent acid refluxate into the esophagus and reduce the esophageal stimulation.<sup>21–23</sup> In addition, glycosaminoglycans (GAGs) have been recently shown to play a potential role in the pathophysiology of GERD, as they are involved in maintaining the integrity of esophageal mucosa, with some formulations having demonstrated a positive impact on symptom relief.<sup>13,24</sup> Some authors have assessed the association of these components to achieve additive or even synergistic effects on symptom improvement. An important concern relates to the bioavailability of these products in the esophageal mucosa, leading to the proposal of bioadhesive formulations.<sup>25</sup>

Finally, the physicians' suboptimal adherence to GERD guidelines remains a concerning issue in clinical practice. In fact, despite the availability of evidence-based recommendations for the diagnosis and management of GERD, many healthcare providers continue to deviate from these guidelines.<sup>26,27</sup> Given the wide range of diagnostic and therapeutic possibilities in clinical practice, we aimed to conduct a comprehensive survey among GPs and different medical specialists to investigate the medical approaches to patients reporting GERD symptoms and their characteristics. We also analyzed the potential role of adjunctive pharmacological treatments in PPIs-non-responder patients with GERD symptoms.

## Methods

### *Study design and variables*

The present analysis focused on a survey carried out across a large sample of gastroenterologists, GPs, and ENT specialists who agreed to participate in continuing medical education courses with the title 'REGERD – real-world evidence in the management of patients with gastroesophageal reflux disease'. The courses were carried out between February 2022 and January 2023. The reporting of this study conforms to the Consensus-Based Checklist for Reporting of Survey Studies (CROSS).<sup>28</sup>

All physicians were asked to complete a survey (Supplemental Files 1 and 2) on their consulting population with symptoms and/or diagnostic findings related to the GERD spectrum. Patients were eligible for inclusion if they were between

18 and 75 years of age and suffered from symptoms suggestive of GERD in accordance with international guidelines for GERD diagnosis and management.<sup>9</sup>

The survey was conducted to collect anonymized demographic and anthropometric data from clinical cases observed by different physicians, such as sex, age, weight, and body mass index (BMI). The presence of comorbidity was considered and the presence of arterial hypertension, dyslipidemia, diabetes, obesity, and chronic obstructive bronco-pneumopathy were registered, as well as other less frequent comorbidities. The endoscopic findings, as well as pH-monitoring results, when available, were collected. Moreover, patients were asked about any types of habits previously associated with GERD symptoms (i.e. eating large meals, eating faster than usual, not chewing properly, having dinner later than usual, lying down immediately after meals, wearing belts or very tight clothing at the waist, performing physical activity immediately after meals).

Symptoms reported by patients were subdivided into typical and extraesophageal, and their severity as well as their impact on the quality of life were assessed using the GERD Impact Scale (GIS) questionnaire.<sup>29</sup> This tool comprises nine questions designed to investigate the frequency of the most prevalent GERD symptoms experienced in the previous week. In addition, it examines their impact on sleep, dietary habits, work performance, and the discomfort resulting from therapeutic interventions. The Reflux Symptom Index (RSI)<sup>30</sup> was also evaluated to identify patients suffering from symptoms associated with LPR.

All therapies administered for GERD were recorded and classified as PPIs, prokinetic agents (i.e. levosupiride, cisapride, benzamide, metoclopramide), and histamine 2 antagonists. Adjunctive pharmacological treatments were also considered and were classified into GAGs, acid neutralizers, alginate-based compounds, and a combination of these products. The addition of a specific bioadhesive mixture was also addressed.

The physician was also investigated regarding the therapeutic modifications prescribed after the first evaluation which were considered as follows: new drugs in addition to PPIs, dose escalation,

change in PPIs, and prescription of adjunctive pharmacological treatments as maintenance monotherapy.

### Statistical analysis

IBM SPSS Statistics, Release Version 25.0 (SPSS, Inc., Chicago, IL, USA, www.spss.com) was used for the statistical analysis. The Kolmogorov–Smirnov test was performed to determine if the variables were normally distributed. The median and interquartile range (IQR) were used to express the outcomes of continuous variables. Contingency tables were used to show the frequency and proportion of ordinal and nominal variables in the population. When comparing continuous variables between different patient groups, nonparametric Kruskal–Wallis or Mann–Whitney tests were used. Pearson’s chi-square ( $X^2$ ) test and Spearman’s rank correlation index were applied to analyze the relationship between nominal variables and continuous variables. The Bonferroni correction was used to fit tests for all pairwise comparisons. A generalized multivariate model (GML) was used to adjust the GSI and RSI of patients considering sex, age, BMI, and referring specialists or GP as fixed factors and covariates. Data were weighted for the numerosity of each adjunctive pharmacological treatment considered using weighted least squares.

### Results

A total of 212 physicians agreed to participate in the survey, and 151 completed the online form. Most of them were otolaryngologists ( $n=70$ , 46.4%), followed closely by gastroenterologists ( $n=58$ , 38.4%), while 23 (15.2%) were GPs. The data provided by these three categories of doctors resulted in a total inclusion of 6211 patients who were suffering from symptoms suggestive of GERD ( $n=2492$  collected by gastroenterologists;  $n=738$  collected by GPs; and  $n=2981$  collected by ENT specialists).

Gender was equally distributed (male: 3137, 50.5%; female: 3074, 49.5%) without differences among the attending physicians and the median age was 51 (IQR 41–61) years, although patients evaluated by the gastroenterologists were slightly but significantly younger (49 years, IQR 38–60,  $p<0.0001$ ). The median BMI was close to overweight cutoff (25.1, IQR 22.8–27.8 kg/m<sup>2</sup>) with

slightly, but significantly, lower values in patients belonging to GPs (24.2, IQR 22.1–26.6 kg/m<sup>2</sup>) than gastroenterologists and ENT specialists (25.1, IQR 22.7–27.8 kg/m<sup>2</sup> and 25.4, IQR 23.0–28.4 kg/m<sup>2</sup>,  $p<0.0001$  and  $p=0.001$ , respectively).

The prevalence of at least one comorbidity was higher in the GP group ( $n=291$ , 39.4%) and the ENT specialist group ( $n=1188$ , 39.9%) than in the group of gastroenterologists ( $n=919$ , 36.9%). Table 1 reports the general characteristics and comorbidities of all patients.

### Symptoms and management of patients

Patients who reported typical symptoms were 3324 (53.5%), while extraesophageal symptoms were reported by 2887 (46.5%). Patients referred to the ENT evaluation exhibited extraesophageal symptoms more frequently ( $n=1598/2981$ , 53.6%) than those followed by gastroenterologists ( $n=953/2492$ , 38.2%) and GPs ( $n=336/738$ , 45.5%), with  $p$  values of  $<0.0001$  for both comparisons.

The detailed analysis of the patient’s symptoms according to GSI and RSI is illustrated in Tables 2 and 3. The total GSI was 9 (IQR 6–12) points, with higher values recorded in patients followed by gastroenterologists (9, IQR 6–12 points) and GPs (9, IQR 7–12 points) than ENT specialists (8, IQR 6–11 points). On the other hand, the mean RSI was  $12.42 \pm 7.24$  but higher values were observed in the ENT group  $14.28 \pm 6.93$ ,  $p<0.0001$ ) than GP and gastroenterologist groups ( $10.36 \pm 6.36$  and  $10.81 \pm 7.30$ ,  $p<0.0001$ ). Overall, patients with a high risk of LPR (RSI  $\geq 13$ ) were 3076 (49.5%), with higher prevalence in the ENT group (1842, 61.8%) than in GP (260, 35.2%) and gastroenterologist groups (974, 39.1%). Figure 1 shows the correlation index between different symptoms and indicators of quality of life. Chest pain was the most frequently reported symptom associated with a negative impact on diet, work activity, and the need for additional drugs to those already prescribed, while the poorest quality of sleep was associated with hoarseness or odynophagia.

Throughout a 10-year time period, a total of 2232 out of 6211 patients (35.9%) underwent esophagogastroduodenoscopy. Among these patients,

**Table 1.** Demographic and clinical characteristics of the whole population.

Features	Whole population (n=6211)	Patients of gastroenterologists (n=2492)	Patients of general practitioners (n=738)	Patients of ENT specialists (n=2981)	<i>p</i> 1 versus 2	<i>p</i> 1 versus 3	<i>p</i> 2 versus 3
Demographic features							
Male sex, <i>n</i> (%)	3137 (50.5)	1226 (49.2)	391 (53.0)	1520 (51.0)			
Median age, <i>n</i> (range) years	51 (41–61)	49 (38–60)	51 (44–63)	54 (44–63)			
Median BMI, <i>n</i> (range) kg/cm <sup>2</sup>	25.1 (22.8–27.8)	25.1 (22.7–27.8)	24.2 (22.1–26.6)	25.4 (23.0–28.4)			
Presence of comorbidities							
Yes	2398 (38.6)	919 (36.9)	291 (39.4)	1188 (39.9)	0.04	0.03	
Unknown	301 (4.8)	136 (5.5)	45 (6.1)	120 (4.0)	3	7	
Type of comorbidity							
Hypertension	1481 (61.8)	563 (61.3)	179 (61.5)	739 (62.2)			
Dyslipidemia	698 (29.1)	278 (30.3)	94 (32.3)	326 (27.4)			
Diabetes	607 (25.3)	241 (26.2)	87 (29.9)	279 (23.5)			
Obesity	647 (27.0)	253 (27.5)	80 (27.5)	314 (26.4)			
COPD	303 (12.6)	93 (10.1)	35 (12.0)	175 (14.7)		0.001	
Other	313 (13.1)	142 (15.5)	47 (16.2)	124 (10.4)		0.025	0.031
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ENT, specialist: otolaryngologists; <i>p</i> , <i>p</i> value.							

the majority (1,351, 60.5%) had a single endoscopy during this study period, while 772 (34.6%) underwent the examination two or three times but only 109 (4.9%) received more than four endoscopies. No statistically significant differences were found among the different physicians. The main endoscopic findings were erosive esophagitis (366/2232, 16.4%) and Barrett's esophagus (128/2232, 5.7%). Grade A erosive esophagitis was found in 330 patients (14.8%), while no lesions were detected in 1152/2232 (51.6%) patients. The endoscopic presence of hiatal hernia was observed in 61.5% (*n*=1372/2232) of the observations. A total of 442/6211 patients (7.1%) were investigated with reflux monitoring during the same 10-year time period. Table 4 shows the endoscopic and reflux testing results divided according to the physician

group considered. Patients referred to the gastroenterologists had worse endoscopic and reflux monitoring findings compared to those referred to GPs and ENT specialists.

#### *Therapies and association with symptoms severity*

Overall, PPIs were used by 3025 patients (48.7%) with lower use by ENT specialists (1269/2492, 42.6%, *p*<0.0001) than GPs (389/738, 52.7%, *p*<0.0001) and gastroenterologists (1367/2492, 54.9%, *p*<0.0001). Anti-H<sub>2</sub> drugs were administered only in 149 (2.4%) patients and no differences were observed among specialists. Prokinetics drugs were used in a few patients (291, 4.7%) with a significantly higher use among GPs (61/738, 8.3%) than gastroenterologists

**Table 2.** Symptoms reported by patients according to GSI are subdivided according to the physician group considered.

Features	Whole population (n=6211)	Patients of gastroenterologists (n=2492)	Patients of general practitioners (n=738)	Patients of ENT specialists (n=2981)	p 1 versus 2	p 1 versus 3	p 2 versus 3
<b>Chest pain</b>							
Everyday/often	1490 (24.0)	863 (34.6)	190 (25.7)	437 (14.7)	<0.0001	<0.0001	<0.0001
Sometimes/never	4721 (76.0)	1629 (65.4)	548 (74.3)	2544 (85.3)			
Sub-total	1 (0-1)	1 (0-2)	1 (0-2)	0 (0-1)			
<b>Heartburn</b>							
Everyday/often	2288 (36.8)	1192 (47.8)	258 (35.0)	838 (28.1)	<0.0001	<0.0001	<0.0001
Sometimes/never	3923 (63.2)	1300 (52.2)	480 (65.0)	2143 (71.9)			
Sub-total	1 (0-2)	1 (1-2)	1 (1-2)	1 (0-2)			
<b>Regurgitation</b>							
Everyday/often	2561 (41.2)	1131 (45.4)	316 (42.8)	1114 (37.4)	<0.0001	<0.0001	<0.0001
Sometimes/never	3650 (58.8)	1361 (54.6)	422 (57.2)	1867 (62.6)			
Sub-total	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)			
<b>Epigastric pain</b>							
Everyday/often	2295 (37.0)	1063 (42.7)	335 (45.4)	897 (30.1)	<0.0001	<0.0001	<0.0001
Sometimes/never	3916 (73.0)	1429 (57.3)	403 (54.6)	2084 (69.9)			
Sub-total	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)			
<b>Odynophagia or hoarseness</b>							
Everyday/often	2077 (33.4)	760 (30.5)	210 (28.5)	1107 (37.1)	<0.0001	<0.0001	<0.0001
Sometimes/never	4134 (66.6)	1732 (69.5)	528 (71.5)	1874 (62.9)			
Sub-total	1 (0-2)	1 (0-2)	1 (0-2)	1 (1-2)			
<b>Sleep</b>							
Everyday/often	1586 (25.5)	638 (25.6)	211 (28.6)	737 (24.7)			
Sometimes/never	4625 (74.5)	1854 (74.4)	527 (71.4)	2244 (75.3)			
Sub-total	1 (0-2)	1 (0-2)	1 (1-2)	1 (0-1)			
<b>Diet</b>							
Everyday/often	1313 (21.1)	620 (24.9)	142 (19.2)	551 (18.5)	0.002	<0.0001	
Sometimes/never	4898 (78.9)	1872 (75.1)	596 (80.8)	2430 (81.5)			
Sub-total	1 (0-1)	1 (0-1)	1 (1-1)	1 (0-1)			
<b>Work</b>							
Everyday/often	793 (12.8)	412 (16.5)	92 (12.5)	289 (9.7)	0.008	<0.0001	
Sometimes/never	5418 (87.2)	2080 (83.5)	646 (87.5)	2692 (90.3)			
Sub-total	1 (0-1)	1 (0-1)	1 (0-1)	1 (0-1)			

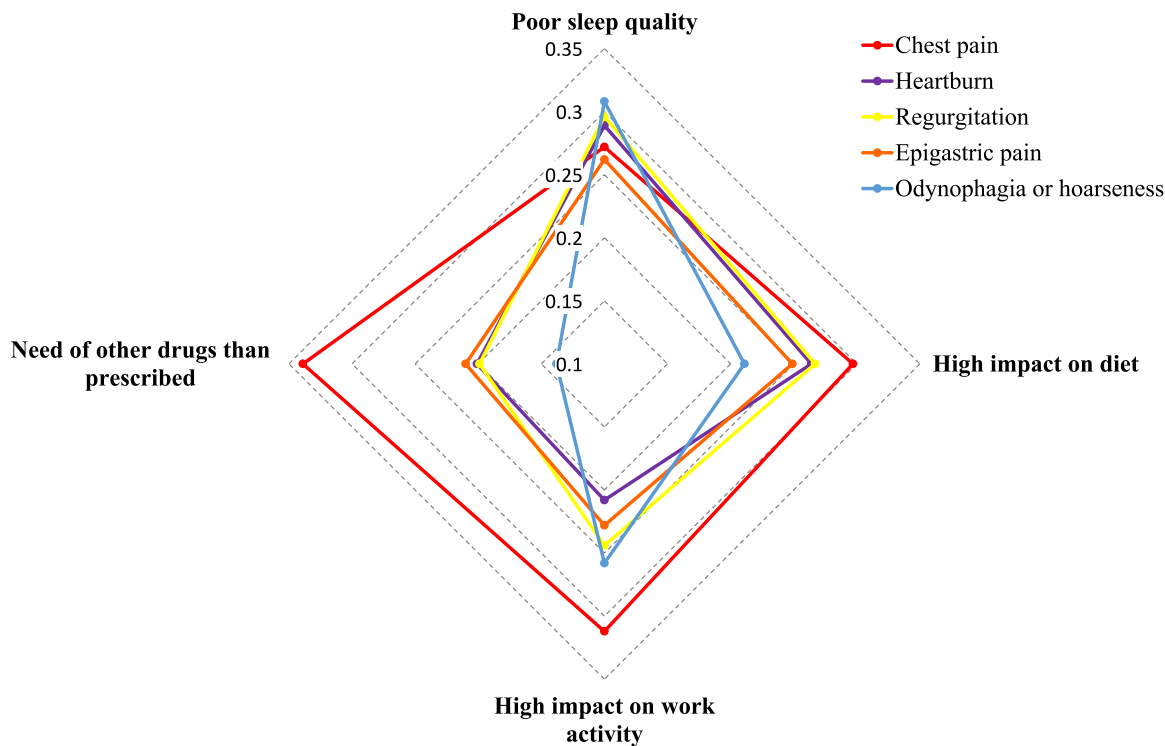
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**Table 2.** (Continued)

Features	Whole population (n=6211)	Patients of gastroenterologists (n=2492)	Patients of general practitioners (n=738)	Patients of ENT specialists (n=2981)	<i>p</i> 1 versus 2	<i>p</i> 1 versus 3	<i>p</i> 2 versus 3
Therapy							
Everyday/often	830 (13.4)	446 (17.9)	85 (11.5)	299 (10.0)	<0.0001	<0.0001	
Sometimes/never	5381 (86.6)	2046 (82.1)	653 (88.5)	2682 (90.0)			
<i>Sub-total</i>	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)			
Total GSI score	9 (6–12)	9 (6–12)	9 (7–12)	8 (6–11)		<0.0001	<0.0001
ENT specialist, otolaryngologists; GSI, GERD Impact Scale; <i>p</i> , <i>p</i> value.							

**Table 3.** Symptoms reported by patients according to RSI are subdivided according to the physician group considered.

Symptoms and scores	Whole population (n=6211)	Patients of gastroenterologists (n=2492)	Patients of general practitioners (n=738)	Patients of ENT specialists (n=2981)	<i>p</i> 1 versus 2	<i>p</i> 1 versus 3	<i>p</i> 2 versus 3
Hoarseness or a problem with your voice	1.22 ± 1.17	0.95 ± 1.11	0.87 ± 0.95	1.53 ± 1.19		<0.0001	<0.0001
Clearing your throat	1.72 ± 1.24	1.40 ± 1.19	1.27 ± 1.00	2.10 ± 1.22	0.014	<0.0001	<0.0001
Excess throat mucus or post-nasal drip	1.39 ± 1.24	1.19 ± 1.17	1.00 ± 0.98	1.65 ± 1.30	0.001	<0.0001	<0.0001
Difficulty swallowing food, liquid, or pills	1.12 ± 1.13	0.95 ± 1.08	0.97 ± 1.08	1.30 ± 1.15		<0.0001	<0.0001
Coughing after a meal or after lying down	1.51 ± 1.25	1.28 ± 1.22	1.43 ± 1.15	1.72 ± 1.27	<0.0001	<0.0001	<0.0001
Breathing difficulties or choking episodes	0.67 ± 1.00	0.57 ± 0.95	0.70 ± 1.05	0.74 ± 1.02	0.001	<0.0001	
Troublesome or annoying cough	1.53 ± 1.29	1.28 ± 1.27	1.36 ± 1.22	1.78 ± 1.27		<0.0001	<0.0001
The sensation of something sticking in your throat or a lump in your throat	1.58 ± 1.32	1.34 ± 1.24	0.98 ± 1.08	1.93 ± 1.34	<0.0001	<0.0001	<0.0001
Heartburn, chest pain, indigestion, or stomach acid coming up	1.69 ± 1.21	1.85 ± 1.22	1.78 ± 1.20	1.54 ± 1.18		<0.0001	<0.0001
RSI-total	12.42 ± 7.24	10.81 ± 7.30	10.36 ± 6.36	14.28 ± 6.93		<0.0001	<0.0001
RSI ≥ 13	3076 (49.5)	974 (39.1)	260 (35.2)	1842 (61.8)		<0.0001	<0.0001
ENT specialist, otolaryngologists; RSI, Reflux Symptom Index; <i>p</i> , <i>p</i> value.							



**Figure 1.** Bivariate correlation coefficient ( $r$ ) between different symptoms and determinants of quality of life.

(136/2492, 5.5%) and ENT specialists (94/2981, 3.2%). Table 5 shows all adjunctive pharmacological treatments subdivided according to PPI administration. No statistically significant differences were observed between patients on-PPI and off-PPI therapies.

We performed a Generalized multivariate model (GML) to evaluate the association between different non-pharmacological anti-GERD therapies and the severity of symptoms measured with GSI and RSI in the subgroup of patients already treated with PPIs (Supplemental Tables 1 and 2). Figure 2(a) shows the adjusted GSI score for each non-pharmacological anti-GERD therapy and Figure 2(b) shows the statistical significance of pairwise comparison among each non-pharmacological therapy for GERD. We found that patients treated with a combination of anti-reflux drugs had statistically significantly lower GSI than patients who assumed only one anti-reflex therapy or PPI-alone. Figure 3(a) shows the adjusted RSI score for each non-pharmacological anti-GERD therapy and Figure 3(b) shows the pairwise statistical significances. We found that drugs containing alginate (i.e. alginate alone and alginate with GAGs) were associated with lower RSI

scores than acid neutralizers. Moreover, this analysis shows significant association between higher GSI score and higher BMI [odds ratio (OR): 1.023, 95% CI: 1.012–1.035,  $p < 0.0001$ ] and older age (OR: 1.022, 95% CI: 1.021–1.023,  $p < 0.0001$ ), likewise higher RSI scores were associated with the same variables (BMI: 1.107, 95% CI: 1.067–1.148,  $p < 0.0001$ ; age: 1.05, 95% CI: 1.026–1.067,  $p < 0.0001$ ). Conversely, in a multivariate model, no associations were found between GSI and RSI with the type of physician, gender, the presence of comorbidities, history of upper gastrointestinal surgery or cholecystectomy, and bad behavioral habits (Supplemental Tables 1 and 2).

#### *Patients' management after the first evaluation*

A new drug in addition to PPIs was prescribed in 1461 patients, although the gastroenterologists administered an additional drug more frequently than GPs and ENT specialists (706, 36.6% versus 130, 22.1% and 625, 26.9%, respectively, with  $p < 0.0001$ ). Moreover, the dose escalation and the change of PPI molecules were proposed more frequently by gastroenterologists (498, 25.8% and 380, 19.7%, respectively) than GPs (105,



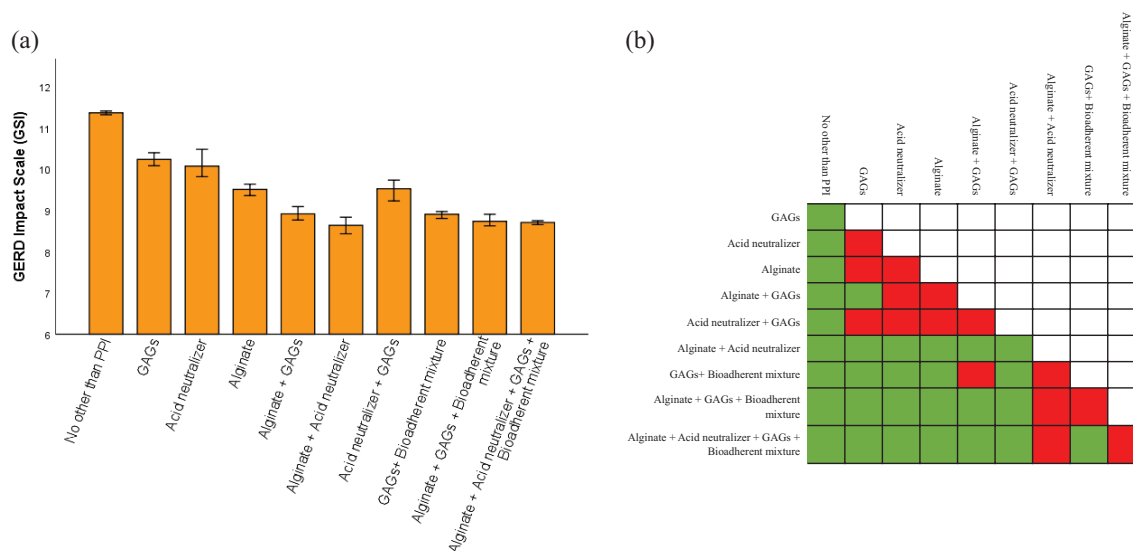
**Table 4.** The endoscopic and 24-h pH-monitoring results are subdivided according to the physician group considered.

Characteristics	Whole population (n=6211)	Patients of gastroenterologists (n=2492)	Patients of general practitioner (n=738)	Patients of ENT specialists (n=2981)	p 1 versus 2	p 1 versus 3	p 2 versus 3
Number of patients who underwent EGD in the last 10 years							
No	3657 (58.9)	1245 (50.0)	474 (64.2)	1938 (65.0)	<0.0001	<0.0001	
Yes	2232 (35.9)	1154 (46.3)	223 (30.2)	855 (28.7)	<0.0001	<0.0001	
Unknown	322 (5.2)	93 (3.7)	41 (5.6)	188 (6.3)	0.025	<0.0001	
Number of EGD							
Once	1351 (60.5%)	669 (58.0)	137 (61.4)	545 (63.7)			
Two or three times	772 (34.6%)	422 (36.6)	79 (35.4)	271 (31.7)			
More than three times	109 (4.9%)	63 (5.5)	7 (3.1)	39 (4.6)			
Endoscopic findings in patients who underwent EGD							
Erosive esophagitis	915 (41.0)	510 (44.2)	116 (52.0)	289 (33.8)	0.013	<0.0001	<0.0001
Barrett's esophagus	128 (5.7)	52 (4.5)	14 (6.3)	62 (7.3)		0.014	
No lesions	1016 (45.5)	523 (45.3)	83 (37.2)	410 (48.0)	0.042		<0.0001
Unknown	136 (6.1)	42 (3.6)	7 (3.1)	87 (10.2)		<0.0001	<0.0001
Grade of erosive esophagitis according to LA classification							
A	330 (34.7)	211 (39.3)	30 (25.2)	89 (30.1)	0.004	0.008	0.011
B	256 (26.9)	150 (27.9)	30 (25.2)	76 (25.7)			
C	102 (10.7)	69 (12.8)	12 (10.1)	21 (7.1)		0.020	
D	8 (0.8)	6 (1.1)	0 (0)	2 (0.7)			
Unknown	256 (26.9)	101 (18.8)	47 (39.5)	108 (36.5)	<0.0001	<0.0001	
Diagnosis of hiatal hernia							
No	674 (30.2)	420 (36.4)	77 (34.5)	177 (20.7)		<0.0001	<0.0001
Yes	1372 (61.5)	685 (59.4)	140 (62.8)	547 (64.0)		0.040	
Unknown	186 (8.3)	49 (4.2)	6 (2.7)	131 (15.3)		<0.0001	<0.0001
Number of patients who performed reflux monitoring in the last 10 years							
No	5248 (84.5)	2123 (85.2)	662 (89.7)	2463 (82.6)	0.005	0.024	
Yes	442 (7.1)	244 (9.8)	22 (3.0)	176 (5.9)	<0.0001	<0.0001	
Unknown	521 (8.4)	125 (5.0)	54 (7.3)	342 (11.5)	0.034	<0.0001	
EGD, esophagogastroduodenoscopy; ENT specialist, otolaryngologists; p, p value; LA, Los Angeles.							

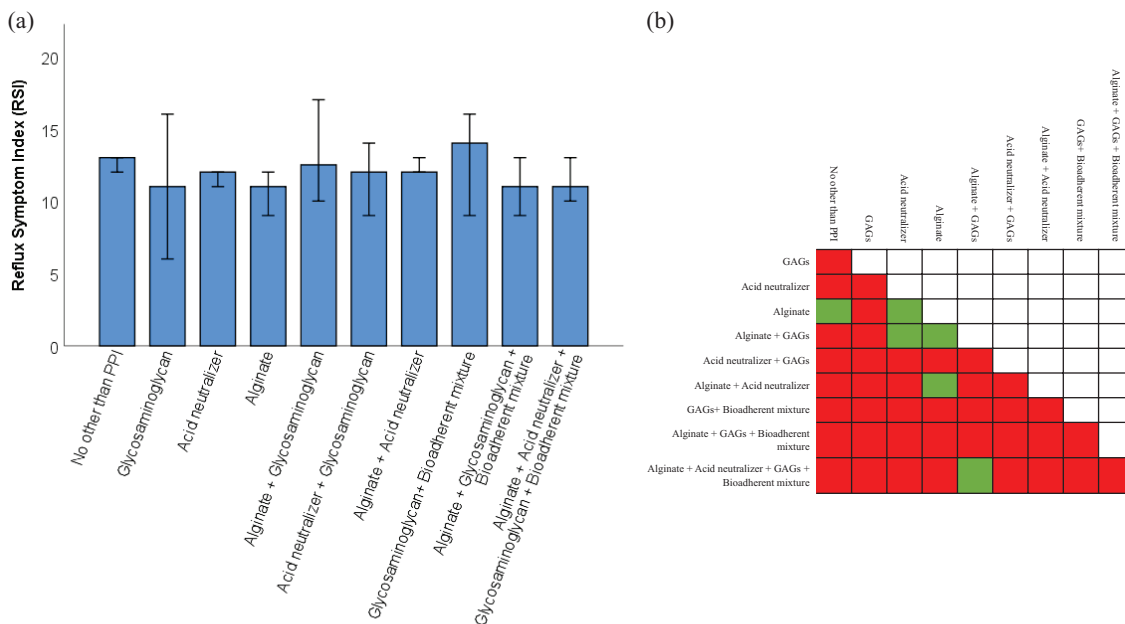
**Table 5.** Additional pharmacological treatments are subdivided according to PPI administration.

Anti-Reflux compounds	Off-PPI (n=3186)	On-PPI (n=3025)	p
Glycosaminoglycan	12 (0.4)	54 (1.8)	<0.0001
Acid neutralizer	36 (1.1)	53 (1.8)	0.039
Alginate-based compounds	91 (2.9)	155 (5.1)	<0.0001
Alginate-based compounds + glycosaminoglycan	176 (5.5)	165 (5.5)	
Acid neutralizer + glycosaminoglycan	66 (2.1)	59 (2)	
Alginate + acid neutralizer	148 (4.6)	165 (5.5)	
Glycosaminoglycan + bioadhesive mixture	212 (6.7)	278 (9.2)	<0.0001
Alginate + glycosaminoglycan + bioadhesive mixture (E-Gastral)	268 (8.4)	289 (9.6)	
Alginate + acid neutralizer + glycosaminoglycan + bioadherent mixture (M-ADESYL)	1083 (34)	854 (28.2)	<0.0001

*p*, *p* value; PPI, proton-pump inhibitor.



**Figure 2.** Adjusted values of GSI in a generalized linear multivariate model are subdivided according to different additional pharmacological therapies (a) and statistical significance of pairwise comparisons according to the Kruskal–Wallis test and after Bonferroni correction (b). Green cells are statistically significant with  $p < 0.05$ . GSI, GERD Impact Scale.



**Figure 3.** Adjusted values of RSI in a generalized linear multivariate model are subdivided according to different additional pharmacological therapies (a) and statistical significance of pairwise comparisons according to the Kruskal–Wallis test and after Bonferroni correction (b). Green cells are statistically significant with  $p < 0.05$ . RSI, Reflux Symptom Index.

17.9% and 79, 13.5%) and ENT specialists (349, 15.0% and 185, 8.0%). An additional pharmacological treatment was administered as maintenance monotherapy in 1427 patients, and it was more frequently proposed by GPs (198, 33.7%) and ENT specialists (811, 34.9%) than by gastroenterologists (418, 21.6%).

## Discussion

This study aimed to investigate the medical approaches employed by physicians from different medical specialties in managing patients with symptoms of GERD and to analyze their characteristics. A multidisciplinary approach to patients suffering from GERD symptoms involves collaborative care from gastroenterologists, ENT specialists, dietitians, and GPs, thus ensuring a comprehensive strategy that addresses not only the diagnostic management, the treatment of symptoms and complications but also involves the practical application of all the recommendations deriving from international guidelines.<sup>13,31</sup>

We observed that patients who were commonly referred to gastroenterologists had more severe

symptoms and worse endoscopic findings than those managed by GPs and ENT specialists. The current medical literature is consistent with our findings, as a comprehensive survey revealed that gastroenterologists assist the highest percentage of patients experiencing reflux symptoms, and, in general, their patients exhibit more severe symptoms compared to those treated by other physicians.<sup>32</sup> These findings highlight the pivotal role of gastroenterologists in managing GERD, particularly in cases with more aggressive symptoms and more complex clinical presentations as they can offer specialized expertise in diagnostic procedures, such as endoscopy and pH-impedance monitoring, in medication management, and, when necessary, they can balance the risk and benefit ratio of surgical therapies.<sup>33–35</sup> We feel that the referral of patients with severe symptoms to gastroenterologists suggests that these individuals experienced symptoms challenging for GPs and other specialists to manage, prompting them to seek specialized care in gastroenterology.<sup>36</sup> Unfortunately, a large proportion of patients underwent upper endoscopy more than once during a 10-year follow-up. This result contrasts with current recommendations for the management of GERD, where

endoscopy should only be advised in the presence of persistent symptoms in individuals who do not respond to PPI challenges or exhibit worrisome features. A single high-quality endoscopy should not need further periodic evaluations in the context of GERD when complications are not found and alarm features are not present.<sup>9</sup> On the other hand, a few systematic reviews with meta-analyses have reported a significant association between GERD and the risk of esophageal and head–neck cancers.<sup>37,38</sup> It is well known that GERD can lead to Barrett’s esophagus, a condition associated with a risk of esophageal neoplastic progression of 0.1%–0.5% per year.<sup>39</sup> This risk is, however, quite low, and current guidelines do not recommend screening endoscopy in patients without clear risk factors.<sup>40–42</sup> Regarding the association of GERD with head–neck cancers, which can represent a significant challenge in managing patients with GERD, especially those with LPR, these data mainly come from case–control studies with a low level of evidence, not strong enough to be fully included in structured surveillance guidelines.<sup>38</sup> We believe that our results stem from the application of current guidelines, which tend to be more restrictive at present in recommending endoscopic evaluation.

In the intricate management of GERD, numerous risk factors have previously been linked to the severity of symptoms. These factors include a history of surgery, improper behavioral patterns such as starting physical activity immediately after meals or going to bed right after eating, as well as unusual dietary measures, among others.<sup>43,44</sup> In our analysis conducted in a large number of patients, the severity of symptoms measured with GSI and RSI was independently associated with higher BMI and older age, and the statistical significance was not reached for many other factors in the multivariate model. We feel that an individualized behavioral and dietary approach supervised by qualified specialists could be useful in managing GERD symptoms rather than poorly outlined measures based on popular belief.

On the other hand, the type of presenting symptoms among patients referred to gastroenterologists, GPs, and ENT specialists was different in our analysis, with the last group of specialists encountering more frequently patients with extraesophageal symptoms. Indeed, patients experiencing chronic cough, laryngitis, and upper airway disorders suspected of GERD are

generally referred to an ENT specialist.<sup>45</sup> After a thorough evaluation, the ENT specialist can categorize the patient as having extraesophageal symptoms of GERD and initiate the necessary diagnostic procedures to reach a certain diagnosis.<sup>46</sup> In our study, this result is further supported by the evidence of higher RSI scores observed among patients managed by ENT specialists. In fact, patients with a high risk of LPR were more prevalent in the ENT specialist group (61.8%) than in the GP (35.2%) and gastroenterologist (39.1%) groups. The diagnostic workup conducted by ENT specialists in GERD patients often involves the use of techniques such as laryngoscopy, which can help to address laryngeal and throat-related complications.<sup>47</sup> Unfortunately, the sensitivity and specificity of these tools appeared low in several studies, and the ENT endoscopic examination could be also influenced by inter-observer interpretation. Moreover, the RSI showed poor reliability as a diagnostic tool in GERD patients, as it may not consistently reflect the full spectrum of symptoms and their severity associated with this complex condition.<sup>48,49</sup>

Interestingly, according to our analysis, each reflux-like symptom impacts differently on the quality of life, and we observed that chest pain had the highest correlation with a reduced quality of life influencing diet, work activity, and the need for additional therapy to control the symptom. The medical literature reports that among all GERD symptoms, non-cardiac chest pain could be both physically and emotionally distressing, causing persistent discomfort and anxiety, and it was previously associated with impaired quality of life.<sup>9,50</sup> On the other hand, worse quality of sleep was more correlated with odynophagia or hoarseness. Hoarseness and the quality of sleep share a mutual link that can significantly impact one’s overall well-being. This symptom is often associated with vocal strain or could underline medical conditions other than GERD and further justifies the need for a multidisciplinary approach in the management of GERD-related symptoms.<sup>51</sup>

An important result of this study is to provide a picture of additional pharmacological treatments in patients with reflux symptoms on PPI therapy, achieved using a confounder-adjusted generalized linear multivariate model. Overall, additional drugs that contained two or more anti-reflux active compounds were independently associated

with lower GSI scores than the mono-therapeutic ones. These findings are consistent with several studies highlighting that a combination of different compounds with anti-reflux or antiacid drugs is more effective than controlling esophageal acid exposure in GERD patients.<sup>15,52–55</sup> Moreover, the addition of a bioadhesive mixture to the pharmacological formulation seems to provide an advantage in terms of both symptom severity and impact on quality of life. It is known that an important limitation of the medications that promote anti-reflux and enhance barrier integrity is the short-term efficacy due to the physiological clearing mechanism of the esophagus.<sup>56,57</sup> The use of viscosity regulators, such as polyvinylpyrrolidone, guar gum, xanthan gum, carrageenan, and pectin, could enhance the effect of other well-established anti-reflux drugs.<sup>58</sup>

Finally, another notable result regards the different management of patients managed by a gastroenterologist, ENT specialist, and GP. The correct management of patients with symptoms of GERD who do not respond to initial treatment with PPI requires a dose optimization or the shift to another molecule of the PPI class.<sup>9</sup> Our analysis found that gastroenterologists were more familiar with PPI dose escalation or switching in class than GPs or ENT specialists.

It is important to acknowledge that the generalizability of our findings may be affected by potential variations in physician practices and patient populations. Moreover, the reliability of a survey and its comprehensiveness may be compromised by factors such as self-reporting bias which should be considered when interpreting the results. Nevertheless, the strength of the analysis, which drew from a comprehensive survey of patients under the care of various physicians, underscores its statistical power and ability to provide valuable insights into diverse medical practices.

In conclusion, this study highlights the importance of a multidisciplinary approach to managing GERD, revealing variations in patient profiles in accordance with the physician's speciality. Patients referred to ENT specialists exhibit more severe extraesophageal symptoms, whereas those seen by gastroenterologists present more complex GERD, often characterized by significant endoscopic findings. The management strategies employed by gastroenterologists respect more closely established GERD guidelines. The use of

additional therapy for PPIs is possible and the concurrent use of multiple agents appears to enhance efficacy. Further studies with prospective designs are needed to confirm our findings.

## Declarations

### *Ethics approval and consent to participate*

According to the Italian Medicines Agency det. 20/03/2008 on retrospective observational studies on anonymous data, preemptive approval by an ethics committee was not mandatory and the need for informed consent was waived. Given that the survey collected anonymous data, was not referable to specific individuals, and was not performed in hospitals or other healthcare settings, approval by one or more ethical committee(s) was not requested. Informed consent could also not be obtained because the identity of patients was unknown. The protocol, in the form of an educational project, was approved by the National Agency for Regional Health Services (AGENAS, id ECM: 5310-329114) and conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All survey participants provided informed consent and agreed to be mentioned in the Supplemental Material.

### *Consent for publication*

All patients provided written informed consent.

### *Author contributions.*

**Andrea Pasta:** Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

**Filippo Pelizzaro:** Conceptualization; Data curation; Formal analysis; Methodology; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

**Elisa Marabotto:** Conceptualization; Data curation; Formal analysis; Methodology; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

**Francesco Calabrese:** Methodology; Resources; Writing – review & editing.

**Elena Formisano:** Methodology; Resources; Writing – review & editing.

**Shirin Djahandideh Sheijani:** Methodology; Resources; Writing – review & editing.

**Giovanni Brandimarte:** Methodology; Resources; Writing – review & editing.

**Giampiero Manes:** Methodology; Resources; Writing – review & editing.

**Antonietta Gerarda Gravina:** Methodology; Resources; Writing – review & editing.

**Edoardo Vincenzo Savarino:** Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – original draft; Writing – review & editing.

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#### Competing interests

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#### Availability of data and materials

The data underlying this study are available within the manuscript and supplementary materials. Further information is available upon reasonable request.

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#### Supplemental material

Supplemental material for this article is available online.

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