

# Real-world prevalence of endoscopic findings in patients with gastroesophageal reflux symptoms: a cross-sectional study



## Authors

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## ABSTRACT

**Background and study aims** Data regarding endoscopic findings and symptom correlation in patients with gastroesophageal reflux disease (GERD) symptoms are largely limited to single-center experiences. We performed a nationwide study to examine the association between patient-reported GERD symptoms and clinically relevant endoscopic findings.

**Patients and methods** Using the National Endoscopic Database, we retrospectively identified all esophagogastroduodenoscopies (EGDs) performed for GERD symptoms from 2000 to 2014. Patients were categorized into three symptom groups: 1) typical reflux only (R); 2) airway only (A); and 3) both R and A (R+A). Outcomes were the point prevalence of endoscopic findings in relation to patient-reported GERD symptom groups. Statistical analyses were performed using R.

**Results** A total of 167,459 EGDs were included: 96.8% for R symptoms, 1.4% for A symptoms, and 1.8% for R+A symptoms. Of the patients, 13.4% had reflux esophagitis (RE), 9.0% Barrett's esophagus (BE), and 45.4% hiatal hernia (HH). The R+A group had a significantly higher point prevalence of RE (21.6% vs. 13.3% and 12%;  $P < 0.005$ ) and HH (56.9% vs. 45.3% and 38.3%;  $P < 0.005$ ) compared to the R or A groups, respectively. The R group had a significantly higher point prevalence of BE compared to the A or R+A groups, respectively (9.1% vs. 6.1% and 6.1%,  $P < 0.005$ ).

**Conclusions** On a national level, patients experiencing R+A GERD symptoms appear more likely to have RE and HH, while those with only R symptoms appear more likely to have BE. These real-world data may help guide how providers and institutions approach acid-suppression therapy, set thresholds for recommending EGD, and develop management algorithms.

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## Introduction

Gastroesophageal reflux disease (GERD) is a common medical condition with highly variable clinical presentations [1,2]. The esophageal or “typical” symptoms of GERD include heartburn and acid regurgitation. The extra-esophageal symptoms, also referred to as “atypical” symptoms, include cough, hoarseness, asthma, and/or chest pain [3]. These symptoms may disrupt daily functioning, diminish quality of life, and place a significant economic burden on the healthcare system [4]. Furthermore, untreated GERD can lead to complications such as erosive reflux esophagitis (RE) and Barrett’s esophagus (BE), both of which can require invasive intervention, and the latter being a metaplastic precursor to esophageal adenocarcinoma [5].

Existing data regarding mucosal and anatomical findings, as determined by esophagogastroduodenoscopy (EGD), in patients with typical and atypical symptoms of GERD are generally limited by small sample size and/or single-center experiences. We aimed to determine, based on a nationwide, multicenter endoscopic database, the overall symptom correlation with and real-world prevalence of clinically relevant endoscopic findings in patients reporting typical and/or atypical GERD symptoms.

## Patients and methods

### Data source

The National Endoscopic Database (NED) is part of the Clinical Outcomes Research Initiative (CORI) established to study the national utilization and endoscopic outcomes across all gastroenterology practices in the United States. The NED contains de-identified data from a compendium of both inpatient and outpatient endoscopy centers. Participating sites use a standardized computerized report generator to create all endoscopic reports and the data files are transmitted electronically to the central repository located in Portland, Oregon, United States.

### Ethical considerations

Because the NED contains de-identified and publicly available data, it does not require institutional review board approval.

### Study population

We queried the NED to identify all EGDs performed with the primary indication of “GERD symptoms” between 2000 and 2014 among patients aged 18 years and older. Patients with prior esophageal or gastric surgery were excluded. Esophagogastroduodenoscopies performed for patients without documented GERD symptoms were used as a comparator.

### Symptom definitions

Typical/reflux (R) symptoms were defined as heartburn and regurgitation. Atypical/airway (A) symptoms were defined as cough, asthma, hoarseness, and/or chest pain [6–8]. Symptom groups were classified as R only, A only, and R+A. The symptoms in all groups were reported by the patients themselves based on a standardized questionnaire checklist.

## Study outcomes and variables

The primary outcome was the point prevalence of the following endoscopic findings – RE (graded as per the Los Angeles classification), BE, and hiatal hernia (HH) from 2000 to 2014 in the United States – and their respective relationship to the three symptom groups [4].

Study variables consisted of those available in the NED, namely—age, gender, race, and endoscopy setting.

### Statistical analysis

Continuous variables were reported as means  $\pm$  standard deviations, while categorical variables were reported as proportions or percentages. Chi-squared tests were used to analyze and compare categorical variables between symptom groups. Statistical analysis was performed using R statistical software version 3.2.2. A two-tailed  $P < 0.05$  was considered statistically significant.

## Results

### Overall characteristics and symptom prevalence

A total of 167,459 unique EGDs were performed for reflux symptoms – of which 96.8% were for R symptoms, 1.4% for A symptoms, and 1.8% for R+A symptoms (► **Fig. 1**). Overall, the majority of patients were women (51.7%) and White (83.7%). Mean patient age was 54.9 years  $\pm$  14.3 years. Compared to other symptom groups, patients who reported A symptoms were significantly older, while those who reported R symptoms were significantly more likely to be men (all  $P < 0.005$ ) (► **Table 1**).

### Endoscopic findings

Overall, 13.4% of patients (22,491) were found to have RE, 9.0% (15,078) were found to have BE, and 45.4% (76,044) were found to have HH.

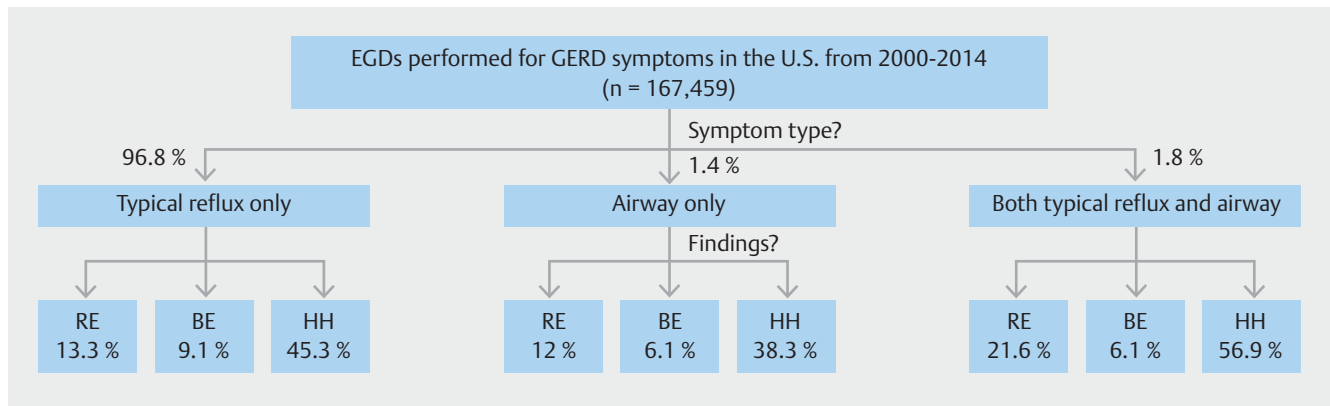
### Correlation between GERD symptoms and endoscopic findings

#### Reflux esophagitis

Patients who reported R+A symptoms had a significantly higher prevalence of RE (21.6%, versus 13.3% and 12.0%;  $P < 0.005$ ) as well as severe RE (3.1% versus 1.9% and 1.9%;  $P > 0.005$ ) compared to patients in the R or A symptom groups, respectively. There was no significant difference in RE prevalence between patients in the R symptom group compared to the A symptom group ( $P < 0.005$ ) (► **Table 2**).

#### Barrett’s esophagus

Patients who reported R symptoms had a significantly higher prevalence of BE compared to patients in the other symptom groups (9.1%, versus 6.1% and 6.1%,  $P < 0.005$ ) (► **Table 2**).



► **Fig. 1** Flow diagram summarizing the three symptom groups and the point prevalence of endoscopic findings, namely reflux esophagitis (RE), Barrett's esophagus (BE), and hiatal hernia (HH), in each symptom group.

► **Table 1** Patient and procedural characteristics for EGDs performed for gastroesophageal reflux disease (GERD) symptoms as a function of symptom group.

	Reflux symptoms only (R) n = 16,2127 (96.7%)	Airway symptoms only (A) n = 2,370 (1.4%)	Reflux and airway symptoms (R + A) n = 2,962 (1.8%)	P value
Age in years (mean)	54.7	60	57	<0.01
Gender (male)	48.7%	37.6%	36.5%	<0.01
Race				<0.01
▪ White	84.6%	89.2%	87.5%	
▪ Hispanic	7.2%	3.7%	4.9%	
▪ African American	5.1%	4.0%	5.3%	
▪ Asian	1.3%	1.2%	1.2%	
▪ Native American	1.0%	0.8%	0.3%	
▪ Others	0.9%	1.1%	0.6%	
Site type				<0.01
▪ Community	77.3%	88.9%	92.3%	
▪ Military/Veteran Affairs hospitals	12.1%	4.3%	0.8%	
▪ University	9.3%	6.2%	1.0%	
▪ Health maintenance organizations	1.4%	0.7%	0.3%	

EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease.

### Hiatal hernia

Patients who reported R + A symptoms had a significantly higher prevalence of HH (56.9%, versus 45.3% and 38.3%,  $P < 0.005$ ) compared to patients in the R or A symptom groups, respectively (► **Table 2**).

### Discussion

In this population-based study using the CORI NED, 167,459 EGDs among adult patients with R, A, or R + A symptoms were examined. Overall, we found that 13.4% of patients had RE,

9.0% BE, and 45.4% HH. On EGD, patients with both R + A symptoms by comparison had the highest point prevalence of RE (21.6%) and HH (56.9%), whereas those with A symptoms alone had few specific EGD findings. Moreover, we found that the overwhelming majority of patients undergoing EGD (96.8%) had R symptoms, and it was patients with R symptoms who had the highest point prevalence of BE (9.1%) on EGD. This study provides real-world, nationwide information regarding the endoscopic correlates of GERD symptom groups (R, A, and R + A), data that had previously been unavailable or incompletely characterized. Given the prevalence of GERD symptoms in

► **Table 2** Endoscopic findings based on gastroesophageal reflux disease (GERD) symptom group.

	Reflux symptoms only (R)	Airway symptoms only (A)	Reflux and Airway symptoms (R + A)	P value
Reflux esophagitis <sup>1</sup>	13.3 %	12 %	21.6 %	<0.005
▪ Grade 0	87.4 %	88 %	78.4 %	<0.005
▪ Grade A-B (mild)	11.4 %	10 %	18.5 %	<0.005
▪ Grade C-D (severe)	1.9 %	1.9 %	3.1 %	<0.005
Barrett's esophagus	9.1 %	6.1 %	6.1 %	<0.005
Hiatal hernia	45.3 %	38.3 %	56.9 %	<0.005

<sup>1</sup> Esophagitis graded as per the Los Angeles classification system.

clinical practice and their potential management implications, we anticipate that these study findings will have significant clinical relevance.

Of the three symptom groups, those who reported R + A symptoms were more likely to have RE as well as severe RE on endoscopy as compared to those who reported either R or A symptoms alone. These findings suggest that a patient with R + A symptoms will likely have increased underlying mucosal inflammation on endoscopy. Previous studies alluded to this finding but were underpowered to identify it and/or were conducted in pediatric populations [9, 10]. This increased likelihood of endoscopically-evident RE in the R + A group, serving as a method of risk stratification, is important for treatment and management as it may inform how aggressively providers may approach acid suppression in such patients as well as the threshold used to refer for endoscopic assessment if symptoms respond incompletely to medical therapy. Although clinical symptoms alone are an indication for treatment, diagnostic tests may be warranted for definitive diagnosis in patients with persistent symptoms and to exclude complications. EGD is the most utilized diagnostic test in this regard. Previous studies have found that one third of patients with GERD have macroscopic evidence of esophageal mucosal injury—significantly higher than our finding of only 13.4% in all EGDs [4]. Thus, on the basis of this nationwide study, the prevalence of RE may not be as high as previously suggested.

BE was even less common than RE overall, present in only 9.0% of all EGDs. It was significantly less prevalent in the A and R + A groups compared to the R group (6.1 % and 6.1 % vs. 9.1%). This is reassuring, given that BE warrants increased frequency of endoscopic surveillance. It also allows clinicians to be wary of, and appropriately triage, patients presenting with R symptoms alone. In a prior cross-sectional study of patients presenting with airway symptoms to an otolaryngology clinic, 58% of patients with BE (19) had both R + A symptoms, 30% (10) had only A symptoms, and 6% isolated R symptoms [3]. It also found that the stigmata of GERD were more strongly correlated with disease chronicity than severity [3]. The current study, with a much larger patient sample, also demonstrated no association between airway symptoms and evidence of BE. However, as data on chronicity of symptoms are not available in

the CORI NED, we could not determine this nature of the disease.

We were intrigued to find that patients with R + A symptoms had more severe RE while BE was more common only in those with R symptoms. This suggests that severe RE may not necessarily be a required prelude to BE, but rather, part of a compendium of other risk factors leading to BE [11, 12]. These findings merit further investigation.

The relationship between HH and GERD has been a subject of debate. It is currently understood that both HH and the lower esophageal sphincter play important roles in GERD symptomatology [13]. In this study, HH was the most common diagnosis, existing in 56.4% of all EGDs, which supports the notion of its role in the pathogenesis of GERD.

Similar to our findings, in prior studies, the most reliable GERD symptoms were heartburn, regurgitation, and non-cardiac chest pain, but unfortunately the first two have poor sensitivity (30%–76%) and specificity (62%–96%) [5]. Cough and throat clearing have a low probability of objective association with GERD according to an ambulatory impedance-pH study of 267 patients [14]. Likewise, asthma, change in voice, chronic laryngitis, and other extra-esophageal manifestations have no clear causal association with GERD [15–17].

This study benefits from a number of strengths. The large number of patients comprising our sample adds significant power. In addition, the multicenter nature by which data in the NED are collected provides information from a variety of clinical and geographical settings and makes our findings generalizable to a wide range of clinical practice locations; in addition, the NED is derived from a variety of gastroenterology practice types, with the majority from community-based settings, simulating a real-world view of endoscopic practices. The standardization and quality control inherent to the NED are also significant strengths of our study, as the database has been used as the primary endoscopic data source for numerous other published studies [18–20].

Despite the strengths of utilizing a large nationwide database, this study also has associated limitations. One of the most notable limitations is the lack of information within the NED regarding proton pump inhibitors (PPIs) or other acid-suppressing agents. Given the prevalence of PPI use in clinical practice, lack of information on PPI use represents a potential con-

founder. Moreover, owing to the lack of granular data in this national database, we were unable to stratify patients according to body mass index, symptom type/severity, and/or identify those with previous *Helicobacter pylori* infection – all of which may impact our studies results. Also, we acknowledge that the prevalence of RE, BE, and HH may depend on background parameters, which also have the potential to act as a confounder, and therefore warrants further investigation. In addition, we analyzed the data assuming clinical practice guidelines were uniformly adhered to and that EGDs were performed in these patients because they were refractory to empiric treatment or had other appropriate indications. Moreover, there was no information on endoscopist expertise, nor were endoscopic findings histologically confirmed; this is relevant considering that GERD-related endoscopic stigmata present high interobserver variability, and confirmatory diagnosis is ultimately based on histology. Also, some patients likely had combined endoscopic findings which could not be accounted for, given the lack of such granular data in this dataset. Finally, not all practice sites in the United States participate in the CORI, leaving open the possibility of selection bias (particularly from non-academic centers).

## Conclusions

In conclusion, this study provides a large analysis of real-world endoscopic findings in patients reporting typical and atypical GERD symptoms. Important associations were identified between patient-reported symptoms and clinically relevant endoscopic findings. These results importantly underscore the complex relationship between typical and atypical reflux symptoms and endoscopic mucosal findings and thereby aid in developing algorithms to triage for ancillary testing in an evidence-based fashion. In addition, while these data have the potential to impact how aggressively providers approach acid suppression as well as the threshold used to make an endoscopic assessment upon refractory disease, prospective studies are warranted to better correlate endoscopic findings to patient symptomatology.

## Competing interests

The authors declare that they have no conflict of interest.

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