

# Upper Endoscopy in Patients with Extra-Oesophageal Reflux Symptoms: A Multicentre Study

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## Keywords

Upper gastrointestinal endoscopy · Extra-oesophageal reflux · Gastro-oesophageal reflux · Diagnostic yield

## Abstract

**Background:** There are no evidence-based recommendations for performing upper gastrointestinal endoscopy (UGIE) in patients with extra-oesophageal symptoms of gastro-oesophageal reflux disease (GORD). However, UGIEs are often performed in clinical practice in these patients. We aimed to assess the prevalence of gastro-oesophageal lesions in patients with atypical GORD symptoms. **Methods:** Patients complaining of at least one extra-oesophageal GORD symptom and undergoing UGIE in seven centres were prospectively enrolled. Clinically relevant lesions (Barrett's oesophagus, erosive oesophagitis, gastric precancerous conditions, peptic ulcer, cancer, and *H. pylori* infection) were statistically compared between groups regarding GORD symptoms (atypical vs. both typical and atypical), type of

atypical symptoms, age, and presence of hiatal hernia. **Results:** Two hundred eleven patients were enrolled (male/female: 74/137; mean age: 55.5 ± 14.7 years). Barrett's oesophagus was detected in 4 (1.9%), erosive oesophagitis in 12 (5.7%), gastric precancerous conditions in 22 (10.4%), and *H. pylori* infection in 38 (18%) patients. Prevalence of clinically relevant lesions was lower in patients with only atypical GORD symptoms (28.6 vs. 42.5%;  $p = 0.046$ ;  $\chi^2$  test), in patients ≤50 years (20 vs. 44.8%;  $p = 0.004$ ;  $\chi^2$  test), and in those in ongoing proton pump inhibitor (PPI) therapy (21.1 vs. 40.2%;  $p = 0.01$ ;  $\chi^2$  test). No clinically relevant lesions were detected in patients ≤50 years, without alarm symptoms, and receiving PPI therapy. Hiatal hernia was diagnosed in only 6 patients with cardiologic and in 41 patients with ear-nose-throat symptoms (11.3 vs. 35.1%;  $p = 0.03$ ;  $\chi^2$  test). **Conclusions:** Clinically relevant lesions are uncommon among young (≤50 years) patients with extra-oesophageal GORD symptoms. Hiatal hernia is not more prevalent in patients with cardiologic symptoms and suspicion of GORD. The usefulness of UGIE in these patients is questionable.

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## Endoscopia alta em doentes com sintomas de refluxo extra-esofágicos: um estudo multicêntrico

### Palavras Chave

Endoscopia digestiva alta · Refluxo extra-esofágico · Refluxo gastroesofágico · Rendimento diagnóstico

### Resumo

**Introdução:** Não existem recomendações baseadas na evidência para realização de endoscopia digestiva alta (EDA) em doentes com sintomas extra-esofágicos da doença de refluxo gastroesofágico (DRGE). No entanto, EDAs são frequentemente realizadas na orientação clínica destes doentes. O nosso objectivo foi avaliar a prevalência de lesões gastro-esofágicas em doentes com sintomas atípicos de DRGE. **Métodos:** Doentes com pelo menos um sintoma extra-esofágico de DRGE e que realizaram EDA em 7 centros foram prospectivamente recrutados. Lesões clinicamente relevantes (esófago de Barrett, esofagite erosiva, condições pré-malignas gástricas, úlcera péptica, cancro e infecção *H. pylori*) foram estatisticamente comparadas entre os grupos tendo em conta sintomas de DRGE (atípicos vs. quer típicos e atípicos), tipo de sintomas atípicos, idade e presença de hérnia do hiato. **Resultados:** Duzentos e onze doentes foram recrutados (H/M: 74/137; Idade média:  $55.5 \pm 14.7$  anos). Esófago de Barrett foi detetado em 4 (1.9%), esofagite erosiva em 12 (5.7%), condições pré-malignas gástricas em 22 (10.4%) e infecção *H. pylori* em 38 (18%) doentes. A prevalência de lesões clinicamente relevantes foi inferior em doentes com apenas sintomas atípicos (28.6 vs. 42,5%;  $p = 0.046$ ; teste de qui-quadrado), doentes com  $\leq 50$  anos (20 vs. 44.8%;  $p = 0.004$ ; teste de qui-quadrado), e nos doentes medicados com iniciadores da bomba de prótons (IBP) (21.1 vs. 40.2%;  $p = 0.01$ ; teste de qui-quadrado). Nenhuma lesão clinicamente relevante foi detectada nos doentes com  $\leq 50$  anos, sem sintomas de alarme e medicados com IBP. Hérnia do hiato foi diagnosticada apenas em 6 doentes com sintomas do tipo cardíaco e em 41 com sintomas ORLs (11.3 vs. 35.1%;  $p = 0.03$ ; teste de qui-quadrado). **Conclusões:** Lesões clinicamente relevantes são incomuns em doentes jovens com sintomas extra-esofágicos de DRGE. Hérnia do hiato não é mais prevalente em doentes com sintomas do tipo cardíaco e suspeita de DRGE. A utilidade da EDA nestes doentes é discutível.

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## Introduction

Upper gastrointestinal endoscopy (UGIE) is a useful procedure for diagnosis, surveillance, or exclusion of relevant gastroduodenal diseases [1]. Therefore, it is widely used in clinical practice for investigating patients with different symptoms, generally scheduled as open-access procedure [2]. Different guidelines on gastro-oesophageal reflux disease (GORD) recommend endoscopy in patients  $>50$  years or with long-lasting ( $>5$  years) symptoms to screening for Barrett's oesophagus [3]. Moreover, UGIE should be performed irrespective of age when alarm symptoms (bleeding, dysphagia, persistent vomiting, anaemia, weight loss) are present [4]. GORD is highly prevalent in the Western countries and its incidence is increasing [5]. Classically, GORD may present with typical (heartburn, regurgitation), extra-oesophageal (laryngeal, pharyngeal, pulmonary, and cardiac) symptoms, or both [6]. According to our knowledge, no official guidelines nor expert-based recommendations suggest performing UGIE in the diagnostic work-up of patients presenting with only extra-oesophageal GORD symptoms [7–11]. Nevertheless, UGIEs are often performed in clinical practice for this indication.

To our knowledge, there are no consistent data on the prevalence of relevant gastro-oesophageal lesions in patients with extra-oesophageal GORD symptoms. Therefore, we designed this study aiming to assess the prevalence of relevant gastro-oesophageal lesions at UGIE in patients with atypical GORD symptoms observed in clinical practice.

## Methods

### Patients

This was a prospective, multicentre study involving seven centres (Bari, Bologna, Foggia, Perugia, Rome-1, Rome-2, Trieste). Consecutive patients complaining of at least one extra-oesophageal GORD symptom, with or without typical symptoms, referred for UGIE from September to December 2018 were invited to participate. Persistent cough, hoarseness, and pharyngeal globus/throat clearing or laryngitis (i.e., ear-nose-throat [ENT] symptoms) or retrosternal pain and palpitations (cardiologic symptoms) were considered as extra-oesophageal GORD symptoms, whilst heartburn or regurgitation as typical GORD symptoms. Dysphagia, anaemia, weight loss, and vomiting were considered as alarm symptoms. Exclusion criteria were (1) age  $<18$  years, (2) patients with only typical GORD symptoms, (3) symptoms already investigated with a previous UGIE, and (4) contraindication to take gastric biopsies.

### Methods

All patients underwent UGIE with antral, incisura angularis, and gastric body biopsies, as in routine practice. Moreover, at least 6 oesophageal biopsies were taken when patients were complaining of dysphagia and no apparent lesions were detected to rule out eosinophilic oesophagitis. Barrett's oesophagus was diagnosed according to endoscopic and histological standard criteria [11] and erosive oesophagitis according to the Los Angeles classification [12]. Peptic ulcer was defined as a deep lesion >5 mm in diameter on gastric or duodenal mucosa. Hiatal hernia was detected when the apparent separation between the squamo-columnar junction and the constriction formed as the stomach traverses the hiatus was greater than 2 cm [13]. The presence of gastric precancerous conditions (atrophy or intestinal metaplasia) and *H. pylori* infection was assessed at histological examination [14]. Oesophageal or gastric cancers were confirmed at histology. Clinically relevant lesions – that is, those affecting patient's management – included Barrett's metaplasia, erosive oesophagitis, erosive gastro-duodenitis, eosinophilic oesophagitis, gastric precancerous conditions, *H. pylori* infection, peptic ulcer, and neoplasia. The use of proton pump inhibitor (PPI) was registered and gathered as ongoing, suspended from at least 2 weeks before, past use (>3 months), and never performed.

### Statistical Analysis

Clinically relevant lesions (Barrett's oesophagus, erosive oesophagitis, gastric precancerous conditions, peptic ulcer, cancer, and *H. pylori* infection) were statistically compared between groups regarding GORD symptoms (atypical vs. both typical and atypical), type of atypical symptoms, age, and presence of hiatal hernia. The rate of frequencies and mean of values were calculated, as appropriate. The  $\chi^2$  test or Fisher's exact test was used to compare differences among sub-groups, as appropriate. The odds ratio (OR) values for differences with their 95% confidence intervals (CI) and the Number-Needed-to-Scope (NNS) were calculated. A *p* value less than 0.05 was considered statistically significant.

### Results

A total of 211 patients were recruited, including 74 males and 137 females, with a mean age of  $55.5 \pm 14.7$  years, with 79 (37.5%) smokers. There were 98 patients complaining of only extra-oesophageal GORD symptoms and 113 with both atypical and typical symptoms (Table 1). A total of 52 (24.6%) patients underwent UGIE while receiving PPI therapy, 36 (17.1%) stopped therapy at least 2 weeks before, 29 (13.7%) had been treated in the past, and 94 (44.6%) never used these drugs. UGIE was prescribed by general practitioners in 86 (40.7%) cases, ENT specialists in 52 (24.6%), gastroenterologists in 54 (25.7%), and cardiologists in the remaining 19 (9%) patients.

At endoscopy, Barrett's oesophagus was detected in 4 (1.9%) patients (C0M1: 3, C0M2: 1, all without dysplasia), erosive oesophagitis in 12 (5.7%) cases (LA-A: 10, LA-B:

**Table 1.** Symptom distribution in the recruited patients

Parameter	N
Atypical GORD symptoms ( <i>n</i> = 211)	cough: 90 hoarseness: 45 pharyngeal bolus: 23 palpitations: 34 retrosternal pain: 19
Atypical GORD symptom duration, months	<3: 21 3–6: 58 >6: 132
Typical GORD symptoms ( <i>n</i> = 113)	heartburn: 68 regurgitation: 16 both: 29
Alarm symptoms ( <i>n</i> = 44)	dysphagia: 29 anaemia: 8 weight loss: 5 vomiting: 2

GORD, gastro-oesophageal reflux disease.

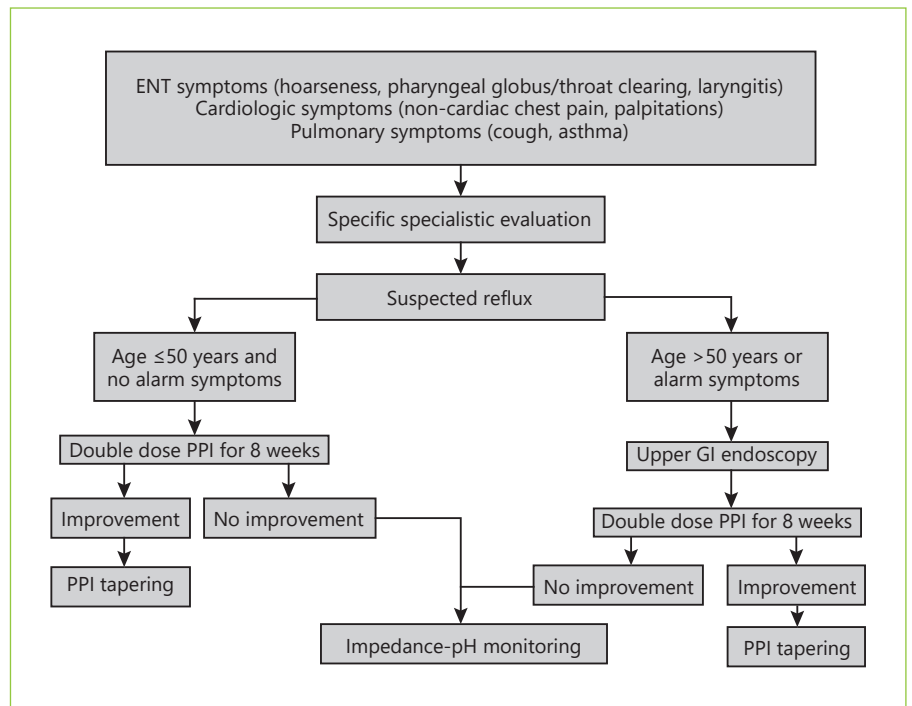
**Table 2.** Characteristics of considered patients (*n* = 211)

Parameter	Only atypical symptoms ( <i>n</i> = 98)	Atypical plus typical symptoms ( <i>n</i> = 113)	<i>p</i> value
Male/female	38/60	36/77	0.3
Mean age $\pm$ SD, years	56.2 $\pm$ 15	54.8 $\pm$ 14.8	0.4
Smoking habit	24	55	0.001
Ongoing PPI therapy	34	18	0.002
Barrett's oesophagus	1	3	0.9
Erosive oesophagitis	2	10	0.03
Hiatal hernia	27	20	0.09
<i>H. pylori</i> infection	16	22	0.9
Intestinal metaplasia	9	13	0.6

PPI, proton pump inhibitor.

1, and LA-C: 1), and hiatal hernia was diagnosed in 47 (22.3%) patients, whilst no cases of eosinophilic oesophagitis, peptic ulcers, and cancers were detected. At histological examination of gastric mucosa, precancerous conditions were present in 22 (10.4%) cases and *H. pylori* infection in 38 (18%) patients.

As shown in Table 2, patients with only extra-oesophageal symptoms underwent UGIE while taking PPI therapy more frequently than those with combined symptoms, whereas they were diagnosed with erosive oesophagitis less frequently. The cumulative prevalence of



**Fig. 1.** Diagnostic algorithm.

clinically relevant lesions was distinctly lower in patients with only extra-oesophageal GORD symptoms as compared to those with combined symptoms (28/98, 28.6% vs. 48/113, 42.5%;  $p = 0.046$ ; OR: 0.54, 95% CI = 0.3–0.96), with an NNS of 15. Similarly, they were significantly lower in patients  $\leq 50$  than in those  $> 50$  years old (15/75, 20% vs. 61/136, 44.8%;  $p = 0.004$ ; OR: 0.3, 95% CI = 0.15–0.59; NNS = 22) and in patients on ongoing PPI therapy (11/52, 21.1% vs. 65/159, 40.2%;  $p = 0.01$ ; OR: 0.3, 95% CI = 0.18–0.8; NNS = 19). In detail, among patients with  $\leq 50$  years and without alarm symptoms ( $n = 61$ ), there were 48 not receiving PPI and 13 in ongoing therapy. A relevant finding was detected in 12 and 0 patients, respectively ( $p = 0.04$ ). Moreover, the manifest signs of GORD (erosive oesophagitis/Barrett) was detected in 13 (11.5%) patients with combined symptoms and only in 3 (3.1%) with only extra-oesophageal symptoms (OR: 4.1, 95% CI = 1.13–14.9;  $p = 0.02$ ; NNS = 10). Prevalence of clinically relevant lesions did not differ between patients with or without hiatal hernia (18/47, 38.1% vs. 42/164, 25.6%;  $p = 0.09$ ). Hiatal hernia was diagnosed in only 6 (11.3%) patients with cardiologic and in 41 (35.1%) patients with ENT symptoms ( $p = 0.03$ ). Moreover, patients with cardiologic symptoms showed the same prevalence of manifest signs of reflux at endoscopy when compared to the other patients (5.5 vs. 7.6%;  $p = 0.7$ ).

## Discussion

A recent systematic review showed that UGIEs are inappropriately prescribed in more than 20% of cases and that the diagnostic yield in inappropriate procedures is distinctly lower as compared to that of appropriate examinations [15]. In addition, inappropriate UGIEs have a negative impact on resources utilization, particularly when considering the very high number of procedures performed annually worldwide. More than 2.5 million UGIEs are performed yearly in Italy, mainly for investigating patients with dyspepsia, typical GORD reflux symptoms, or alarm symptoms [2]. To our knowledge, no guideline suggests performing UGIE in patients with extra-oesophageal GORD symptoms. Therefore, although a high rate of inappropriateness and a low diagnostic yield were foreseeable in this setting, no specific data are available at present.

There are some clinically relevant findings in our study on this topic. We found that the diagnostic yield in patients with only extra-oesophageal GORD symptoms is scarce, and it is distinctly lower than that of patients with concomitant typical symptoms. In detail, the probability of finding a clinical relevant lesion affecting patient's management is reduced by 46% when compared to patients with simultaneous typical GORD symptoms. Similarly, our data showed that the likelihood of finding a rel-

evant lesion is 70% lower when UGIEs are performed in patients with less than 50 years of age, as well as in those receiving PPI therapy, with 22 and 19 more UGIEs needed to discover a relevant lesion, respectively.

Although European and Italian guidelines suggest stopping PPI therapy at least 2 weeks before performing a diagnostic UGIE [3, 4], we found that as many as 1 in every 4 patients was referred for endoscopic examination while taking PPI therapy. In a previous Italian study, 1 in every 2 patients was on PPI therapy when UGIE was performed [16]. There is evidence that an ongoing PPI therapy significantly reduces the probability of finding erosive oesophagitis, gastroduodenal erosions, and *H. pylori* infection [17] and even that of gastric and oesophageal cancer [18]. Noteworthy, in our study, clinically relevant lesions were absent in all young patients with only extra-oesophageal GORD symptoms who performed endoscopy on PPI therapy. On the other hand, we found that as many as 45% of patients were referred for UGIE without having previously performed a 2-month empiric therapy with adequate dose PPI, as suggested by experts [10, 19]. Based on all these observations, a critical reappraisal is needed for physicians in prescribing UGIE in this setting.

The potential role of hiatal hernia and/or GORD in triggering palpitations by stimulating heart innervations has been suggested [20]. A systematic review of 8 observational studies found that patients with GORD had an increased risk of developing atrial fibrillation, but it was impossible to establish a causal relationship based on these studies [21]. Unexpectedly, our data found that the prevalence of both hiatal hernia and endoscopic signs of GORD were not higher (if not lower) in patients referred for cardiologic symptoms. Likewise, an adequate pH-monitoring study, rather than UGIE, would be more appropriate

in these patients to confirm or rule out GORD [10, 19], and a diagnostic algorithm may be proposed (Fig. 1).

Possible limitations of our study are a potential selection bias and the relatively small sample size. Indeed, the study included data of patients who were referred for UGIE in open-access Endoscopic Units, and they may be not representative of other patients with atypical GORD symptoms managed without resorting to an endoscopic examination. The number of patients with only atypical GORD symptoms was near one hundred, so that data of further larger studies might be helpful.

In conclusion, the data of this prospective, multicentre study found that clinically relevant lesions are uncommon among young ( $\leq 50$  years) patients with only extra-oesophageal GORD symptoms. Hiatal hernia is not more prevalent in patients with cardiologic symptoms than in other patients. Therefore, the usefulness of UGIE in these patients is questionable.

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### Statement of Ethics

The study was performed according to the guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000). Each patient consented to anonymously use clinical data. Since no experimental drugs were administered, no adjunctive costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, our Investigational Review Board waived formal review and approval, deeming the study to be an extension of existing clinical practice.

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### Disclosure Statement

The authors have no conflicts of interest to declare.

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