

## Evaluation of the Outcomes of Anti-Reflux Surgery in the Management of Extraoesophageal Symptoms of Gastro-oesophageal Reflux Disease

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### ABSTRACT

**Background** About one third of gastro-oesophageal reflux disease (GORD) patients were found to have atypical or extra-oesophageal symptoms (EOS), which represent a diagnostic and therapeutic challenge. The efficacy of the current treatment strategy used to control these symptoms is still controversial. Anti-reflux surgery has been shown to significantly improve respiratory symptoms associated with GORD.

**Objective:** The aim of the current study was to evaluate the outcomes of laparoscopic fundoplication to control GORD-related EOS.

**Patient and methods:** A prospective cohort study was conducted and included patients diagnosed with GORD with or without EOS or predominant EOS who were referred from Respiratory or ENT Departments. All participants underwent laparoscopic fundoplication surgery. Data about patients' demographics, body mass index (BMI), GORD/EOS presenting symptoms, 24 pH/manometry results, oesophagogastroduodenoscopy findings, perioperative outcomes, quality of life using gastrointestinal quality of life Index (GIQOLI) questionnaire, patient's satisfaction using modified Visick score, and EOS severity using reflux symptom index (RSI) preoperatively, and 6 months postoperatively were collected and statistically analyzed. **Results:** A total number of 103 were included with mean age of 45.6 (SD 8.7) years, and 60% of the study's population was female. Mean BMI was 27.25 (SD 3.6). Heart burn was the main symptoms in all patients (71.9%), while chronic cough was the main EOS (27%). The mean operative time was 96 (SD 19.21) minutes, and mean hospital stay was 1.21 (SD 0.42) day. There was significant improvement in quality of life [65.7 (SD 11.6) and 118 (SD 12.8)] and reflux score [93.76 (SD 0.8) and 1.7 (SD 0.6)], RSI score for EOS [19.89 (SD 14.7) and 4.3 (SD 5.3)] preoperatively and 6 month postoperatively respectively.

**Conclusion** Laparoscopic fundoplication is a feasible option to control EOS associated with GORD with significant improvement of quality of life and reflux symptom index. Further larger studies are still warranted to evaluate the benefits on the long term.

**Keywords:** Chronic cough, Reflux, Fundoplication, Laryngopharyngeal reflux, Extraoesophageal symptoms.

### INTRODUCTION

In the western world, gastro-oesophageal reflux disease (GORD) is a common gastrointestinal pathology with a high prevalence. According to the Montreal Consensus, GORD is a disorder that appears when the stomach's contents reflux into the oesophagus and generate bothersome symptoms and/or consequences <sup>(1)</sup>.

The troublesome symptoms can be oesophageal symptoms as heartburn, regurgitation, dyspepsia with related complications ranging from oesophagitis, strictures, Barrett's esophagus and up to oesophageal adenocarcinoma <sup>(2)</sup>. Extraoesophageal symptoms (EOS) associated with large-scale GORD provide diagnostic and therapeutic challenges since they can affect the mouth, upper airways, and lungs and manifest as asthma, laryngitis, persistent cough, dental erosions, and non-cardiac chest pain <sup>(2)</sup>.

In a large prospective European study, GORD is associated in about 13% of patients with variety of atypical EOS as chronic cough, hoarseness of voice, asthma, sore throat, painful swallowing, and lump sensation in the throat <sup>(3-5)</sup>.

It has been estimated that about 20-60% of patients with GORD will present with atypical symptoms without having typical symptoms of GORD. Therefore,

to rule out other causes, the diagnosis of GORD-related EOS necessitates close coordination amongst experts <sup>(6,7)</sup>.

There is no conclusive test to demonstrate GORD-related EOS. Even though non-acidic and moderately acidic reflux episodes may now be measured using impedance reflux technology, this still does not sufficiently indicate reflux into the pharynx or the airway <sup>(8)</sup>.

Although the presence of pepsin in the bronchoalveolar lavage fluid is thought to be irrefutable evidence of aspiration of stomach contents, this method of diagnosis may not be practical or practicable in many underdeveloped nations <sup>(9,10)</sup>.

Currently, empirical double dose of proton pump inhibitors (PPI), modifying one's diet and way of life are the standard treatment strategy used for management of GORD related EOS, although the efficacy of PPI to control these symptoms was still controversial. It has been demonstrated that anti-reflux surgery considerably reduces the requirement for medication and improves respiratory symptoms related to GORD <sup>(11)</sup>.

The aim of the current study was to evaluate the outcomes of laparoscopic fundoplication to control EOS associated with GORD.

## PATIENTS AND METHODS

A prospective cohort study was conducted and included 103 patients with documented GORD with or without associated EOS or predominant EOS who were referred from Respiratory or ENT Departments, after exclusion of underlying respiratory causes.

**Inclusion criteria:** Patients with continuing GORD symptoms despite a double dose of PPIs were offered surgery as well as young patients who do not preferred to continue on lifelong medical treatment were included.

**Exclusion criteria:** Patients with underlying oesophageal motility disorder were excluded as they were offered other types of antireflux surgery, as well as patients with high BMI more than 35 kg/m<sup>2</sup> or those with EOS symptoms with underlying respiratory or cardiac disorder to limit any confounding factors. We excluded any patient with oesophageal dysmotility to avoid any cofounding factor and we usually offered them partial fundoplication.

All patients underwent 24 PH/ high resolution manometry. The normal values for distal reflux were defined as pH <4, total percentage of time with pH <4 and DeMeester composite score <14.7<sup>(10)</sup>. A score >14.72 was considered abnormal acid reflux.

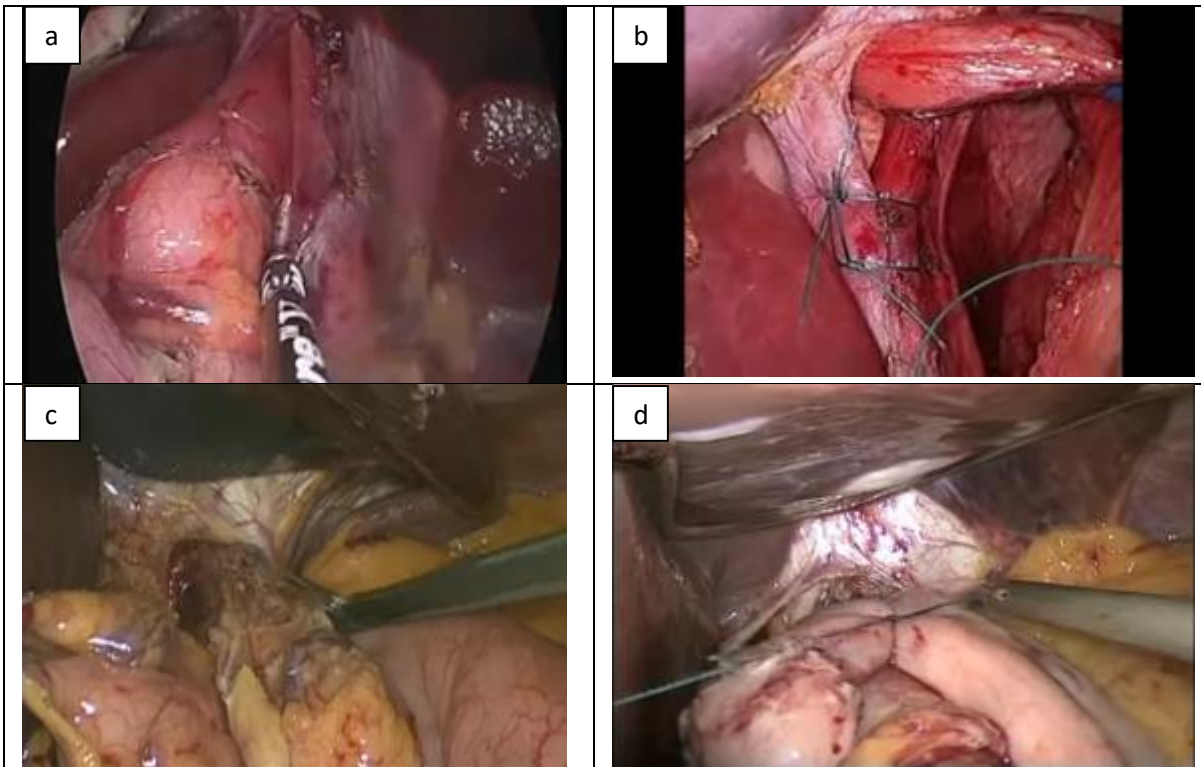
Oesphagogastrroduodenscopy (OGD) was performed for all to evaluate presence of oesophagitis which is considered evidence of reflux for patients who did not tolerate 24ph/manometry, presence of Barrett's oesphageus, and hiatus hernias.

## Surgical Intervention

Laparoscopic Nissen Fundoplication was performed for all patients in Ain Shams University Hospitals, from June 2016 to June 2019. We adopted the French technique where the surgeon operates between the patients' leg, with the assistant standing to the left of the patient. We usually use an energy sealing device to ensure adequate mobilization of the oesophagus and fundus with variable division of short gastric to ensure floppy wrap.

Approximation of 2 pillars of the right crus by non-absorbable sutures posterior to the oesophagus then construction of 360-degree floppy fundoplication wrap (**Figure 1**).

Six hours after surgery, patients began to eat and got their first dose of prophylactic low molecular weight heparin. Unless they were clinically sick, patients were released the following day. All patients received a dietary pamphlet, and follow-up appointments were set up for 1 and 6 months after surgery.



**Figure (1): (a-d)** Intraoperative view of laparoscopic fundoplication. Dissection of left pillar after short gastric division. **(b)** Restoration of adequate intraabdominal esophageal length and crural closure. **(c and d)** Creation of short floppy wrap 360 degree.

**Outcomes**

We collected data about patients’ demographics, body mass index (BMI), GORD/EOS presenting symptoms, 24 pH/manometry results, OGD findings, perioperative outcomes, quality of life using Gastro-Intestinal Quality of life Index (GIQOLI) questionnaire, patient’s satisfaction using modified Visick score (Figure 2), and EOS severity using reflux symptom index (Figure 3) preoperatively and 6 months postoperatively.

Of the symptoms recorded, GORD symptoms as heartburn and regurgitation. As well as EOS as Chronic cough (defined as existing for more than eight weeks duration, with appropriate respiratory investigation to exclude respiratory pathologies), hoarseness of voice, asthma, others like throat clearing, globus sense, sore throat, and dental erosions. Cough was considered due to reflux when it occurred during or within 3 min from an episode of reflux (10).

GIQOLI includes a group of variable questions about GIT symptoms, daily activities, fitness, and psychological status. The score ranges between 0-144 and was calculated by summation of the points of questions where the most desirable option was rated with 4 points and the least desirable option with 0 points (12).

Visick 1	Excellent	No symptoms.
Visick 2	Very good	Mild symptoms, patient considers result perfect.
Visick 3	Good	Mild or moderate symptoms, not controlled by care but not interfering with work or enjoyment of life.
Visick 4	Satisfactory	Moderate symptoms, not controlled by care but only occasionally interfering with work or enjoyment of life. Patient and doctor satisfied.
Visick 5	Unsatisfactory	Moderate or severe symptoms, compromising work or enjoyment of life. Patient and doctor not satisfied.

**Figure (2): Modified Visick classification for Reflux.**

Patients were asked to rank the nine difficulties on a range of 0 (no problem) to 5 (severe problem), with a maximum total score of 45, in the Reflux Symptom Index (RSI), a nine-item questionnaire. For the purposes of diagnosing EOS, a total score of greater than 13 is seen as favorable (13).

Within the last MONTH, how did the following problems affect you?  
0 = no problem, 5 = severe problem

1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucous or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Coughing after you ate or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensations of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
Total						

**Figure (3): Reflux symptom index (RSI).**

**Ethical Consideration:**

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Ain Shams University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

**Statistical Analysis**

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher’s exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and SD, and independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

**RESULTS**

Data of a total number of 103 patients with documented GORD with or without associated EOS or predominant EOS who were referred from respiratory or ENT department after exclusion of underlying respiratory causes were collected and statistically analyzed.

**Table 1** summarizes the sociodemographic data of the included patients.

**Table (1): Patients’ sociodemographic characteristics.**

Age: Mean (SD)	45.6 (8.7)
Gender: N (%)	Male: 41 (40%) Female: 62 (60%)
BMI: Mean (SD)	27.25 (3.6)

Heart burn was the main symptoms in all patients (71.9%), as shown in **Table 2**. Chronic cough existing for more than eight weeks with appropriate respiratory investigation to exclude respiratory pathologies was the main extra-oesophageal presenting symptoms (27%).

**Table (2): GORD/EOS presenting symptoms of the included patients.**

<b>Heart Burn</b>	74 (71.9%)
<b>Regurgitation</b>	56 (54%)
<b>Others (dyspepsia, retrosternal chest pain, dysphagia)</b>	40 (38.8%)
<b>Chronic Cough</b>	28 (27%)
<b>Hoarseness of Voice or Dysphonia</b>	23 (22%)
<b>Exacerbation of Asthma</b>	20 (19.4%)
<b>Others (Globus sensation/ Throat clearing)</b>	13 (12.6%)

The results of distal esophageal PH studies were recorded in 85 patients, as 18 patients could not tolerate the study. The mean number of episodes of reflux in the distal esophagus was 194. The mean percentage of acid exposure time in the distal esophagus with PH below 4 was 12.7 % (SD 3.1). The Mean DeMeester score was 91.77 (SD 22.7). The mean lower oesophageal sphincter (LOS) pressure measured was 5.65 (SD 1.3) where the normal LOS pressure reference was considered between 12-25mmHg.

All patients underwent upper GI endoscopy as part of the preoperative assessment which had identified associated hiatus hernia in 72 (69.9 %) patients of type 1 hiatus hernia in more than 95% of the patients. GORD related complications were also identified where 13 (12.6%) patients had reflux esophagitis, 5 (4.8%) patients with Barret’s oesophagus, and were added to postoperative endoscopic surveillance.

The mean operative time was 96 (SD 19.21) minutes without conversion to open surgery, no mortality, intraoperative, or postoperative complications was recorded with mean hospital stay 1.21 (SD 0.3) day.

There was significant improvement in quality of life [65.7 (SD 11.6) and 118 (SD 12.8)] and Visick reflux score [3.76 (SD 0.8) and 1.7 (SD 0.4)] as shown in **Table 3**, preoperatively and 6 month postoperatively, respectively.

EOS was significantly improved as reflected by RSI score preoperatively and 6 month postoperatively [19.89 (SD 4.8) and 4.3 (SD 1.02)], respectively.

**Table (3): Comparative analysis of Visick reflux scores, quality of life, and RSI preoperative, and six months postoperatively**

Variable	Pre-operative	6 M-Postoperative	P-value	Significance
Visick reflux score	3.76 (SD 0.8)	1.7 (SD 0.4)	P <0.0001	<b>Significant</b>
GIQOLI score	65.7 (SD 11.6)	118 (SD 12.8)	P <0.0001	<b>Significant</b>
RSI	19.89 (SD 4.8)	4.3 (SD 1.02)	P <0.0001	<b>Significant</b>



## DISCUSSION

Short- and Long-term efficacy of anti-reflux surgery to relieve the GORD symptoms and maintain better quality of life in about 88-95% of the patients, has been proven in several reviews <sup>(14)</sup>.

Numerous laryngeal symptoms, including hoarseness, sore throat, painful swallowing, lump in the throat, cough, repeated cleaning of the throat, abundant phlegm, trouble swallowing, and voice fatigue, can be brought on by GORD <sup>(7)</sup>.

Anti-reflux surgery has been shown to significantly improve respiratory symptoms associated with GORD and reduce the need for medications <sup>(11)</sup>.

We aimed in our study to evaluate the outcomes of laparoscopic fundoplication to control the extraesophageal symptoms associated with GORD.

We are presenting a prospective cohort study with follow up 6 months. We included 103 patients with documented GORD with or without associated EOS or predominant EOS who were referred from Respiratory or ENT Departments, after exclusion of underlying respiratory causes. About one-third of our study population had associated EOS, which was mainly chronic cough (27%).

Non-cardiac chest discomfort is the most prevalent symptom among GORD patients (23%), followed by pulmonary signs such bronchitis (14%), asthma (9%) as well as hoarseness (14.8%), globous feeling (7%), and persistent cough in roughly 13% of cases <sup>(3-5)</sup>.

GORD is a multifactorial disease with variable outcomes after laparoscopic fundoplication. In our practice we always follow a strict preoperative protocol to achieve the best outcomes. It is imperative to counsel the patients properly on more than one occasion to explain the procedure and possible postoperative dietary change, understanding their expectations, go through thoroughly preoperative workup to have objective evidence of the reflux.

We don't operate on BMI over 32, and we advised the patient to lose weight ideally to be under BMI 30 as high-rate recurrence in obese patients, we offered partial fundoplication for associated oesophageal dysmotility.

We do routinely 24 PH/ high resolution manometry to have objective evidence of reflex and assess the oesophageal motility. We perform OGD was performed for all to evaluate presence of esophagitis/ Barrett's oesphageus which is considered evidence of reflux for patients who did not tolerate the Manometry or PH studies and also to assess any associated hiatus hernias.

Endoscopically GORD could be erosive reflux disease (ERD) or non-erosive reflux disease (NERD) depending on the presence of erosions on endoscopic examination <sup>(2)</sup>.

PPIs have been used to treat EOS for a long time, however a recent meta-analysis found that there was no

difference in the rate at which PPIs relieved cough symptoms compared to the control group and that there was a significant placebo effect <sup>(15,16)</sup>.

In a Large series of **Silva et al.** <sup>(11)</sup>, which included 400 patients with three-year follow, they concluded that antireflux surgery was effective to relieve and control the GORD symptoms with no statistically significant difference between 6 months and 3 years after the surgery.

We found significant improvement in quality of life [65.7 (SD 11.6) and 118 (SD 12.8)] and reflux score [3.76 (SD 0.8) and 1.7 (SD 0.4)] preoperatively and 6 month postoperatively respectively.

EOS in our study was significantly improved as reflected by RSI preoperatively and 6 months postoperatively [19.89 (SD 4.8) and 4.3 (SD 1.02)], respectively.

One of the most common immediate postoperative side effect of antireflux surgery is temporary dysphagia which gradually improved over six weeks and would persist in about 2-5% of the patients <sup>(17,18)</sup>, temporary dysphagia was typically encountered in about 44% of our patients, however; neither of them has persistent dysphagia beyond 6 weeks.

Numerous studies have investigated how antireflux surgery affects GORD-related respiratory symptoms, and conclude that after laparoscopic fundoplication, significant reduction of the respiratory symptoms associated with GORD was noted 86% of the patients and about 67% remained even asymptomatic <sup>(19, 20-22)</sup>.

**Westcott et al.** <sup>(23)</sup>, whose LPR symptom index improved by 84%. In addition to **Catania et al.** <sup>(24)</sup>, They reported 65% of complete response (patients feeling no symptoms) and 97% improvement in symptoms (reduction >5 points in RSI) after the first month.

**Koch et al.** <sup>(25)</sup> concluded in his cohort study on hundred patients who underwent antireflux surgeries both Nissen and Toupet's fundoplication, suffering from GERD associated EOS as (cough, asthma, hoarseness, and distortion of taste), that Laparoscopic fundoplication is justified and highly recommended in GORD with unusual symptoms resistant to medical intervention. The Toupet's fundoplication, however, could have a less significant impact.

**Patti and Herbella** <sup>(10)</sup> as well as **Hoppo et al.** <sup>(26)</sup> concluded in their studies the same beneficial results of antireflux surgery in patients with chronic cough.

Additionally, in a large metaanalysis conducted by **Tutsumi et al.** <sup>(27)</sup> it yields the same conclusion of significant improvement of the GORD related respiratory symptoms after having antireflux surgery.

Our study is limited with its short-term duration, patient's dropouts, small number of patients, and non-comparative, but is considered one of the few in the literature evaluating the role of anti-reflux surgery in GORD related EOS. Additionally, unavailability of

dual probe pH monitoring for detecting Oro-pharyngeal reflux, was one of the challenges to confirm laryngopharyngeal reflux as well as to correlate cough and episodes of reflux in the lower and upper esophagus.

In conclusion, Laparoscopic fundoplication is a feasible option to control EOS associated with GORD with significant improvement of quality of life and reflux symptom index. Further larger studies are still warranted to correlate cough and episodes of reflux in the lower and upper esophagus and to evaluate the benefits in the long term.

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