



## Laparoscopic antireflux surgery (LARS) is highly effective in the treatment of select patients with chronic cough



Adrian Park, MD, FACS\*, Adam S. Weltz, MD, Zachary Sanford, MD, Alex Addo, MD, MPH, H. Reza Zahiri, DO

Department of Surgery, Anne Arundel Medical Center, Annapolis, MD

### ARTICLE INFO

#### Article history:

Accepted 29 January 2019

Available online 5 April 2019

### ABSTRACT

**Background:** We present the largest single-center study to date of surgical and quality-of-life outcomes among patients treated with laparoscopic antireflux surgery for reflux-associated chronic cough. Extraesophageal manifestations of chronic gastroesophageal reflux are increasingly recognized, among which chronic cough may substantially compromise patient quality of life. Although the benefits of antireflux surgery are well documented in patients with typical symptoms of gastroesophageal reflux disease, less is known about the short-term impact of antireflux surgery on associated chronic cough.

**Methods:** Review of a prospectively maintained database of patients with gastroesophageal reflux disease was conducted, identifying individuals who underwent laparoscopic antireflux surgery between February 2012 and July 2018. Inclusion criteria consisted of identifying manifestations of chronic cough in patients diagnosed with gastroesophageal reflux disease as assessed by preoperative survey in addition to the physiologic diagnosis of pathologic reflux. Patient quality of life was analyzed up to 3 years postoperatively using 4 validated survey instruments: the Reflux Symptom Index, Gastroesophageal Reflux Disease–Health Related Quality of Life, Laryngopharyngeal Reflux Quality of Life, and Swallowing Quality of Life.

**Results:** We identified 232 patients (47 men, 185 women) with symptomatic chronic cough among their manifestations of underlying gastroesophageal reflux disease. Mean age, body mass index, and American Society of Anesthesiologists score were 61.7 years, 28.9 kg/m<sup>2</sup>, and 2, respectively. We observed no 30-day wound-related complications, 17 patients (7.3%) experienced nonwound-related complications, and 2 patients (0.9%) required reoperation. Patients reported significant improvements in chronic cough and other manifestations of gastroesophageal reflux disease during an average of almost 3 years (Reflux Symptom Index –66%, Gastroesophageal Reflux Disease–Health Related Quality of Life –85%, Laryngopharyngeal Reflux Quality of Life –75%, and Swallowing Quality of Life +29%). Complete resolution of chronic cough was observed in 77% of respondents at follow-up, and 71% of postlaparoscopic antireflux surgery patients stopped antireflux medications. Symptom control was accompanied with a high rate of postoperative satisfaction among 71% patients at latest follow-up.

**Conclusion:** Chronic cough associated with gastroesophageal reflux disease after a thorough, objective medical workup can be expected to have an excellent rate of resolution and quality-of-life outcomes after laparoscopic antireflux surgery. A high-volume practice, objective documentation of gastroesophageal reflux disease, and a multidisciplinary approach are key in achieving optimal outcomes.

© 2019 Elsevier Inc. All rights reserved.

### Introduction

Chronic cough is a troublesome and potentially debilitating condition attributable to a variety of underlying pathologies. Studies have estimated patient-reported prevalence to be 1 in 10 individuals, presenting a substantial health care burden both for diagnosis and treatment.<sup>1</sup> The medical resources necessary for evaluation and the time required to identify and treat underlying

Presented at the 2017 Annual Meeting of the Digestive Disease Week/Society for Surgery of the Alimentary Tract.

\* Reprint requests: Adrian E. Park, MD, FACS, Chairman, Department of Surgery, Anne Arundel Medical Center, Professor of Surgery, Johns Hopkins University School of Medicine, Anne Arundel Medical Center, 2000 Medical Parkway, Belcher Pavilion, Suite 106, Annapolis, MD 21401.

E-mail address: [apark@aaahs.org](mailto:apark@aaahs.org) (A. Park).

<https://doi.org/10.1016/j.surg.2019.01.036>

0039-6060/© 2019 Elsevier Inc. All rights reserved.

etiologies present challenges to addressing satisfactory patient quality of life (QOL), with proper assessment often proving to be an extensive and prolonged process.<sup>2,3</sup> A growing body of literature suggests that, in as many as 50% of patients with chronic cough, reflux may play a contributory role in symptomatology and exacerbating manifestations of other comorbid conditions.<sup>4–6</sup>

Gastroesophageal reflux disease (GERD) affects an estimated 18%–28% of the population in the United States, with approximately 25% experiencing pathologic reflux symptoms on a weekly basis.<sup>7,8</sup> From a global health care perspective, reflux disease and associated pathologies represent a tremendous economic burden through direct medical costs numbering in the billions of dollars annually and untold sums spent in health-related losses in individual social productivity.<sup>2,9</sup> Among these costs, greater than half have been attributed to the use of proton pump inhibitors (PPIs), which, although revolutionary in the treatment of GERD, are not without serious and persistent health concerns and only serving to temporize disease severity.<sup>10–12</sup> Evidence supporting the superiority of operative management rather than medical management of GERD in achieving desirable patient outcomes has grown substantially in recent years. Reflux surgery by some accounts has demonstrated subjective improvement in up to 93% of cases, and numerous studies have supported the minimally invasive approach to antireflux surgery as both safe and effective.<sup>13–15</sup> Increasingly long-term data specifically supports persistent symptomatic benefits afforded to those patients undergoing laparoscopic Nissen fundoplication, whereby the recreation of lower esophageal sphincter physiology may afford a return to satisfactory gastrointestinal health.<sup>15</sup>

Traditionally attributed or typical symptoms of pathologic reflux generally manifest as heartburn, acid regurgitation, dysphagia, and occasional substernal chest pain; however, additional less frequently reported or atypical symptoms, such as chronic cough, may occur in a subset of reflux patients.<sup>16</sup> Furthermore, the cost of treating GERD patients with atypical symptoms can be more than five times greater than those with typical symptoms and is associated frequently with additional workup, which may delay diagnosis.<sup>10,17</sup> Currently, less is known about the impact of antireflux surgery on atypical GERD symptoms such as chronic cough compared with the cohort of the well-studied, more typical symptoms of reflux. We report, to our knowledge, the largest study of patients who have undergone the operative treatment of chronic cough by laparoscopic antireflux surgery (LARS). We examined operative and QOL outcomes for these patients and provide recommendations for effective strategies of management.

## Methods

### Study design

We reviewed a prospectively maintained database of more than 1,200 patients who underwent minimally invasive operations for GERD and hiatal hernia at Anne Arundel Medical Center (Annapolis, MD) from February 2012 to July 2018. Cases selected for analysis included individuals 18 years of age or older who presented with chronic cough that was attributed to their gastroesophageal reflux based on an extensive gastrointestinal and otorhinolaryngologic workup and who underwent LARS for the treatment of pathologic reflux. Chronic cough was defined as greater than 8 weeks of patient-defined, troublesome cough symptoms documented on self-assessment QOL survey, specifically a score of  $\geq 2$  of 5 on the Reflux Symptom Index (RSI). RSI is a validated, 9-item outcomes survey instrument used to assess cough related to laryngopharyngeal reflux.<sup>18</sup> Before operative intervention, all patients underwent objective studies to establish the diagnosis of GERD,

characterize its severity, and assess their esophageal motility. These studies included esophagogastroduodenoscopy with biopsies, esophageal impedance testing, dual pH probe monitoring, and high-resolution esophageal manometry. All pH studies were performed during periods in which patients were not currently taking acid-suppressing medications. The standard placement of pH probes to interrogate cough symptoms was 15 cm cranial to the lower esophageal sphincter (LES), although this is usually done as part of a dual pH probe study with a second probe located at 5-cm cranial to the lower esophageal sphincter. Manometric findings were used to help determine whether partial or complete wraps were attempted; however, in this cohort, most patients underwent Nissen fundoplication. Almost all patients presenting with chronic cough had undergone additional consultation earlier with pulmonary and ear, nose, and throat specialists who performed additional respiratory workup, including laryngoscopy and bronchoscopy. Individuals without an objective diagnosis of GERD or who had chronic cough but no objective signs of reflux were not offered LARS and were excluded from this study. Additional reflux symptoms not listed in our study did not serve as exclusion criteria from our analysis. Patient were offered fundoplication based on presenting symptoms, findings on further investigations as recommended in the Society of American Gastrointestinal and Endoscopic Surgeons guidelines,<sup>19</sup> and willingness to comply with perioperative diet recommendation by the clinical dietitian. Patients who required fundoplication as a component of other laparoscopic procedures for treatment of conditions other than GERD were excluded from the study. QOL survey instruments were administered prospectively before LARS and at 1 month, 6 months, and annually after the LARS.

### Operative technique

Generally, our procedure begins with reduction of any intrathoracic portion of the stomach followed by division of the short gastric vessels with an energy device. Mediastinal dissection of the esophagus is undertaken to obtain additional esophageal length and return the gastroesophageal junction back to an intra-abdominal position. An esophageal lengthening procedure in the form of Collis gastroplasty is performed only with shortened esophagus after an unsuccessful dissection to return the gastroesophageal junction to an intra-abdominal position.<sup>20</sup> A retroesophageal crural repair is performed around a 54–56 Blue Silicone Bougie within the esophagus. A subset of patients receive autologous tissue transfer as a falciform ligament flap hiatoplasty, as we have described elsewhere, to buttress their hiatal repairs when primary repair is either not possible or at high risk for failure.<sup>21</sup> A Nissen fundoplication is then performed in standard fashion for those patients with normal esophageal manometry or loose for those with dysmotility.

### Study end point

Patient QOL metrics were analyzed using the following four validated surveys: Reflux Symptom Index (RSI), Gastroesophageal Reflux Disease Health-Related QOL (GERD-HRQL), Laryngopharyngeal Reflux QOL (LPR-HRQL), and Swallowing QOL (SWAL-QOL) instruments.<sup>18,22–24</sup>

The RSI is a validated, 9-item outcomes instrument that documents symptom severity for laryngopharyngeal reflux based on a 5-point scale per question and ranging in total from 0 to 45 points.<sup>18</sup> The instrument was designed to evaluate both typical symptoms of GERD and atypical symptoms, such as difficulty breathing, chronic cough, hoarseness, or globus sensation.

**Table 1**  
Summary of surgical patients and operative outcomes

Patient demographics		<i>N</i> ± SD (min–max)			
<i>N</i>	Sex (male/female)	Age (years)	Body mass index (kg/m <sup>2</sup> )	ASA score	
232	47 (20.3%)/185 (79.7%)	61.7 ± 12.5 (20–89)	28.9 ± 4.8 (18.92–43.2)	2.3 ± 0.5 (1–3)	
Comorbidities				<i>N</i> / <i>%</i>	
Hypertension	120/51.7%	Chronic renal disease	10/4.3%	Stroke (CVA/TIA)	4/1.7%
Hyperlipidemia	109/49.0%	COPD	9/3.9%	Active/recent smoker (< 4 weeks)	3/1.3%
Arrhythmia	28/12.1%	Alcohol abuse	8/3.4%	Myocardial infarction	2/0.9%
Diabetes mellitus	11/4.7%	Barrett's esophagus	9/3.9%	Congestive heart failure	2/0.9%
Coronary artery disease	11/4.7%	Immunosuppression	5/2.2%	Liver disease	1/0.4%
Perioperative Data		<i>N</i> ± SD (min–max)	Postoperative course		<i>N</i> / <i>%</i>
Surgical time (minutes)		95.2 ± 31.2 (36–290)	30-day readmission		2/0.9%
Estimated blood loss (mL)		23.1 ± 29.6 (0–200)	Repeat procedure		2/0.9%
Length of stay (days)		1.5 ± 1.6 (0–17)	Nonwound complications		17/7.3%
Surgical procedure					
Nissen fundoplication (primary)		207/89.2%			
Collis gastroplasty		56/24.1%			
Nissen fundoplication (redo)		18/7.8%			
Toupet fundoplication		7/3.0%			

The 45-point GERD-HRQL tool is a quantitative method of measuring typical symptom severity in GERD patients and was used to assess for any measurable improvement in these symptoms when identified concomitant to atypical symptoms.<sup>22</sup> Scores varied from 0 to 45, similar to the RSI with a similar 5-point scale per question.

The LPR-HRQL questionnaire is another validated survey assessing frequency and severity of vocal changes, dysphonia, cough, and the overall impact of gastric reflux on QOL on a standard 7-point Likert scale.<sup>23</sup> The 43 questions are subdivided into hierarchic categories, including vocal quality, cough, throat clearing, swallow, and overall impact of acid reflux scored to a 10-point maximum per question with a total of 314 points possible.

Last, the SWAL-QOL survey assesses 10 quality-of-life concepts through a 44-item tool with a maximum of 70 points to differentiate normal swallowing behaviors of patients with oropharyngeal dysphagia.<sup>24</sup> The SWAL-QOL is especially sensitive to differences in the severity of clinical dysphagia compared with other survey instruments.

All surveys were collected preoperatively and postoperatively at predetermined follow-up patient encounters at 1 and 6 months and 1, 2, and 3 years follow-up. The primary outcome of our study was to examine patient-reported QOL outcomes for chronic cough, using the 4 validated reflux-specific surveys outlined in the present study. Secondary outcomes of our study included examination of wound-related and non-wound-related complications. Wound-related complications examined included surgical site infection, superficial abscess, deep intraperitoneal abscess, wound dehiscence, recurrence, and need for additional or revision surgery. Non-wound-related complications examined consisted of stroke, myocardial infarction, congestive heart failure, arrhythmia, respiratory failure, pneumothorax, deep venous thrombosis, urinary tract infection, and delay or inability to resume oral intake. Patient mortality and 30-day readmission rates were also documented.

#### Statistical analysis

Study data were collected and managed using electronic data capture tools of the Research Electronic Data Capture (REDCap) hosted at Anne Arundel Medical Center.<sup>25</sup> REDCap is a secure, web-based application designed to support data capture for research studies and provides an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures,

automated export procedures for seamless data downloads to common statistical packages, and procedures for importing data from external sources. Descriptive statistics were used to examine the distribution of each outcome of interest. Where appropriate, Pearson's  $\chi^2$  and Student's *t* tests were used to quantify comparisons between QOL scores before and after LARS. All statistical analyses were performed with SPSS v 20.0 (SPSS, Chicago, IL).

#### Results

A total of 232 patients (47 men, 185 women) reporting chronic cough with underlying GERD were identified in this review of a prospectively maintained reflux database containing more than 1,200 foregut cases performed during the period of this study. Mean age, body mass index, and American Society of Anesthesiologists scores were 61.7 years, 28.9 kg/m<sup>2</sup>, and 2, respectively (Table 1). A total of 87% of patients were on antireflux medication at the time of LARS. Preoperative, 24-hour esophageal pH or impedance studies diagnosed pathologic reflux with a mean DeMeester score of 41.0. For this study, chronic cough was defined by subjective assessment for troublesome cough persisting for a minimum of 8 weeks before surgical consultation. Leading comorbidities among the population of study included hypertension (51.7%), hyperlipidemia (49.0%), arrhythmia (12.1%), diabetes mellitus (4.7%), coronary artery disease (4.7%), and chronic renal disease (4.3%).

Operative correction was performed primarily by fundoplasty, including 201 patients (89%) who underwent Nissen fundoplication and 7 (3.0%) who had a Toupet fundoplication (Table 1). A subset of our patients reported to our center after failing earlier operative corrective efforts at other institutions and required revisional surgery by redo Nissen fundoplication (7.8%). Other techniques included Collis gastroplasty (24.1%) and falciform ligament flap hiatoplasty (2.2%). Mean operative time, estimated blood loss, and duration of hospital stay were 95.2 minutes, 23.1 mL, and 1.5 days, respectively. We observed no postoperative wound-related complications within 30 days after LARS, although there were instances of non-wound-related complications in 17 individuals, including oral intolerance (4, 1.7%), need for antibiotic therapy (3, 1.3%), prolonged ileus (3, 1.3%), urinary tract infection (2, 0.9%), arrhythmia (2, 0.9%), and urinary retention (3, 1.3%; Table 1). Two patients were readmitted within 30 days after LARS, both eventually requiring procedures within 6 months of surgery due to oral

**Table II**  
Summary of QOL metrics

N	% Follow-up	Time point	Significant cough	Currently taking antireflux medications	RSI total score (0–45)	GERD-HRQL total score (0–45)	LPR-HRQL total score (14–314)	SWAL-QOL total score (14–70)	
232	100	Baseline	<i>n</i> 232 % 100	201 86.6	29.9	25.1	121.9	46.5	
213	91.8	1 month	<i>n</i> 27 % 11.6	72 31.0	7.7	2.7	21.9	61.8	
88	37.9	6 month	<i>n</i> 17 % 7.3	18 7.8	7.8	3.0	22.4	60.3	
99	42.7	1 year	<i>n</i> 16 % 6.9	18 7.8	8.9	4.4	23.2	60.6	
89	38.4	2 year	<i>n</i> 21 % 9.1	24 10.3	10.1	4.5	31.3	59.5	
57	24.6	3 year	<i>n</i> 15 % 6.5	19 8.2	10.6	4.7	37.4	57.7	
Average follow-up 31 months		Satisfied: 165/71.1%		Average follow-up score:		10.09	3.85	30.07	59.80
		Neutral: 34/14.7%		Improvement from baseline (raw):		–19.8	–21.3	–91.9	+13.3
Cough resolution 77.2%		Dissatisfied: 26/11.2%		Improvement from baseline (%):		–66.2%	–84.7%	–75.3%	+28.5%

**Table III**  
Patient-reported satisfaction and associated influential factors\*

	Dissatisfied	Satisfied	<i>P</i>	
Number of patients ( <i>n</i> )	26	165		
Age (years)	66.7	60.7	.022 <sup>†</sup>	
Male/female (%)	30.8/69.2	20.0/80.0	.214	
BMI (kg/m <sup>2</sup> )	28.0	28.9	.350	
ASA score	2.4	2.3	.551	
Evidence of hiatal hernia on EGD	10 (38.5%)	70 (42.4%)	.203	
Mean lower esophageal sphincter pressure (LESF) (mmHg)	13.6	21.1	.217	
DeMeester score	49.9	36.2	.172	
Operative time (minutes)	104	94	.140	
Estimated blood loss (mL)	34	19	.026 <sup>†</sup>	
Collis gastroplasty	10 (38.5%)	34 (20.6%)	.058	
Nissen fundoplication	21 (80.8%)	149 (90.3%)	.094	
Toupet fundoplication	0	5 (3.0%)	.359	
Gastrostomy tube placement	1	9 (5.5%)	.705	
Redo Nissen fundoplication	5 (19.2%)	11 (6.7%)	.038 <sup>†</sup>	
Reoperation rate	0	2	.564	
30-day readmission	0	2	.613	
Continuing antireflux medication	12 (46.2%)	40 (24.2%)	.020 <sup>†</sup>	
Risk factor	OR	Low	High	<i>P</i>
Age (years)	0.96	0.92	0.99	.024 <sup>†</sup>
Revisional Nissen fundoplication	0.31	0.10	0.99	.048 <sup>†</sup>
Estimated blood loss (mL)	0.98	0.97	1.00	.037 <sup>†</sup>
Continuing antireflux medication	0.37	0.16	0.87	.023 <sup>†</sup>

BMI, body mass index.

\* Division of variables related to patient outcomes by patient-reported satisfaction as noted during completion of the validated Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) survey instrument.

<sup>†</sup> Indicates significant findings defined as *P* < .05.

intolerance, including GE dilation and endoscopic gastrostomy tube placement.

Baseline QOL instruments confirmed GERD-related symptomatology (RSI 29.9/45, GERD-HRQL 25.1/45, LPR-HRQL 121.9/314, SWAL-QOL 46.5/70; Table II). Of the 232 patients who underwent LARS for the treatment of reflux symptoms, about 77% reported complete resolution of chronic cough during the duration of postoperative follow-up. This involved 61.2% (*n* = 142) of patients who reported complete resolution of both chronic cough and subjective complaints of reflux at the time of latest follow-up, 16.0% (*n* = 37) who reported complete resolution of chronic cough with persistence of subjective complaints of typical reflux symptoms, 14.7% (*n* = 34) who reported persistence of chronic cough with resolution

**Table IV**  
Patient-reported chronic cough resolution and associated influential factors\*

	Persistent cough	Cough resolution	<i>P</i>	
Number of patients ( <i>n</i> )	53	179		
Age (years)	63.6	61.2	.200	
Male/female (%)	13.2/86.8	22.3/77.7	.161	
BMI (kg/m <sup>2</sup> )	27.9	29.2	.077	
ASA score	2.4	2.3	.187	
Evidence of hiatal hernia on EGD	26 (49.1%)	71 (39.7%)	.872	
Mean lower esophageal sphincter pressure (LESF) (mmHg)	18.0	20.1	.623	
DeMeester score	34.7	43.8	.277	
Operative time (minutes)	91	96	.361	
Estimated blood loss (mL)	27	22	.307	
Collis gastroplasty	12 (22.6%)	44 (24.6%)	.948	
Nissen fundoplication	47 (88.7%)	160 (89.4%)	.949	
Toupet fundoplication	1	6 (3.4%)	.655	
Gastrostomy tube placement	1	12 (6.7%)	.214	
Revisional Nissen fundoplication	5 (9.4%)	13 (7.3%)	.494	
Reoperation rate	1	1	.316	
30-day readmission	0	2	.512	
Continuing antireflux medication	20 (37.7%)	43 (24.0%)	.040 <sup>†</sup>	
Risk factor	OR	Low	High	<i>P</i>
Continuing antireflux medication	0.51	0.26	0.97	.042 <sup>†</sup>
Presence of cough <sup>†</sup>	0.43	0.15	1.18	.101

BMI, body mass index.

\* Division of variables related to patient outcomes by patient-reported resolution of chronic cough as noted during completion of the validated Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) survey instrument.

<sup>†</sup> Indicates significant findings defined as *P* < .05.<sup>‡</sup> Logistic regression of the presence of cough on symptom-reflux association analysis as a predictor of postoperative cough resolution.

of subjective complaints of typical reflux symptoms, and 7.6% (*n* = 18) who reported the persistence of both chronic cough and subjective complaints of typical reflux symptoms at the time of latest follow-up. Furthermore, patients who reported taking a PPI for the management of their reflux symptoms decreased their consumption significantly after LARS, and about 72% of post-LARS patients discontinued oral antireflux medications. Patient dissatisfaction with surgery, the postoperative course, or symptom resolution was low, with 71% of patients identifying as satisfied during follow-up.

Analysis of patient QOL measures after LARS was conducted at 1 month to 3 years, demonstrating a sustained and significant

improvement in symptom relief as measured by the 4 validated instruments (RSI –66%, GERD-HRQL –85%, LPR –76%, SWAL +29%; Table II) during the period of study. These findings are consistent with patient satisfaction reports and resolution of reflux-associated cough.

The influence of basic demographic information, investigations, and perioperative outcomes on patient satisfaction are presented in Table III. Dissatisfaction after LARS were more likely with increased age (OR 0.96,  $P = .024$ ), increased estimated blood loss (OR 0.98,  $P = .037$ ), a revisional Nissen fundoplication (OR 0.31,  $P = .048$ ), and need for postoperative antireflux medication usage at latest follow-up (OR 0.37,  $P = .023$ ). In addition, a subgroup analysis to determine factors that influence cough resolution (Table IV) also demonstrated antireflux medication use (OR 0.51,  $P = .042$ ) at latest follow-up was more likely in patients with ongoing chronic cough; however, the presence of cough on analysis of symptom association during ambulatory reflux testing was not predictive of cough resolution (OR 0.43,  $P = .101$ ).

## Discussion

Chronic cough is among the most common symptoms prompting adults to seek medical care in the United States.<sup>26</sup> Despite the protective physiologic functions associated with situationally appropriate cough episodes, chronicity presents a debilitating disorder with profound negative impact on patient psychosocial metrics and QOL.<sup>26</sup> Chronic cough in the adult population can be attributed to numerous etiologies, including post-nasal drip, pathologic insult secondary to chemical irritants (including cigarette smoke), chronic obstructive pulmonary disease, asthma, and pharmacologic reaction (for example angiotensin-converting-enzyme inhibitor therapy). Chronic cough arising from GERD is postulated to be secondary to recurrent irritation by the gastric refluxate. Although thoroughly studied, the exact causal relationship between reflux episodes and extra-esophageal manifestations remains to be defined.

The diagnostic and therapeutic algorithm for GERD with typical symptoms has been well established. Only recently have attempts been made to standardize therapy for symptoms considered atypical, such as chronic cough. The guidelines of the American College of Chest Physicians endorse conservative measures for initial management, including dietary modifications of less than 45 g of fat per day, abstinence from trigger foods (coffee, tea, soda, chocolate, mints, citrus fruits, and alcohol), and cessation of smoking.<sup>27</sup> When medical therapy is necessary, the American College of Chest Physicians recommends PPIs as first-line treatment, although there is increasing evidence for substantial adverse effects associated with chronic PPI therapy.<sup>12,28–30</sup>

The role of operative intervention in management of chronic cough associated with GERD is presently recommended only for those individuals who fail medical management. Optimal  $P$  outcomes after operative intervention in this population are linked strongly to appropriate selection of candidates based on objective measures of reflux and a complete, non-GERD workup to rule out other causes of chronic cough.<sup>31–33</sup> Campos et al<sup>34</sup> demonstrated that an abnormal pH study ( $\text{pH} < 4.0$ ) with associated cough symptoms is the single strongest predictor of success of a LARS in patients with laryngopharyngeal reflux. Patients with a correlation between full-height acid exposure and chronic cough of 80% or greater have demonstrated uniformly the greatest benefit from operative correction with LARS. Upper endoscopy, dual pH probe monitoring, and esophageal manometry, in addition to detailed history and physical exam for the diagnosis of pathologic reflux, serve as the standard for preoperative evaluation in all of our GERD patients. Unique to subjects with chronic cough are airway and

pulmonary evaluations by oropharyngeal exam, laryngopharyngoscopy, bronchoscopy, pulmonary function testing, and allergy workup as indicated by appropriate members of a multidisciplinary team.

Postoperative dietary compliance is also key for optimization of resolution of the symptoms. Patients are counseled by surgeons and our registered dietitians to follow specific guidelines, including small, frequent meals and avoidance of reflux triggers, to ensure durable efficacy of LARS. Diet and the willingness of the patient to comply with postoperative dietary changes are evaluated at the first visit. Patients unwilling to undergo postoperative diet modification are deemed poor operative candidates and are often excluded from operative therapy. Fortunately, this constitutes a small minority of our patients.

We report that minimally invasive antireflux surgery may confer substantial QOL benefits to patients with chronic cough, based on appropriate candidate selection, provided that objective data support a diagnosis of full-height reflux. These findings are consistent with studies of similar populations of chronic cough patients demonstrating major improvement or complete resolution after LARS.<sup>13,35–37</sup> One such study by Kaufman et al<sup>38</sup> followed 128 patients for an average of 53 months after LARS and reported resolution of chronic cough in 65%–75% of operative candidates, but still, one-third of all patients had returned to daily antireflux therapy within the follow-up time in this study. Additional smaller studies by Iqbal et al<sup>39</sup> also demonstrate patient satisfaction with chronic cough resolution by LARS at approximately 90% after a mean follow-up of 53.3 (6–120) months. Another prospective study (of 84 patients) demonstrated substantial resolution of chronic cough in nearly 60% of patients after Nissen fundoplication.<sup>40</sup> To our knowledge, we report the largest study of chronic cough patients who have undergone operative therapy by LARS. To date, we have collected approximately 6 years of follow-up information from our cohort. Predictably, there is a lesser retention rate of study participants at greater follow-up periods. In this study, we sought to report our findings up to 3 years postoperatively. Our study supports the findings of earlier studies; however, our study is unique in the use of 4 validated GERD-specific instruments in evaluating postoperative QOL to capture improvements in atypical and typical symptoms of GERD.

Our study offers some important insights into the relationship between PPI therapy and LARS. Improved response to PPI therapy appears to indicate a favorable response to operative therapy.<sup>41</sup> In addition to acceptable postoperative satisfaction in symptom control, our findings demonstrate that the majority of patients were able to discontinue PPI therapy after LARS. This finding may have important implications, chief among them is the decrease in unnecessary pharmacologic therapy and a decrease in adverse side effects linked to chronic PPI use. General complaints from PPI use may include headache, nausea, abdominal pain, constipation, or diarrhea; however, more severe chronic complaints, such as increased risk of other side effects, such as infectious diseases like pneumonia and *Clostridium difficile* colitis, osteoporosis, cardiac and renal failure, and dementia, have also been reported.<sup>42–48</sup> PPI management of pathologic reflux may be hindered further by cost-effectiveness compared with operative therapy.<sup>11,42–49</sup> We demonstrated that LARS improves patient QOL while decreasing PPI use after LARS, potentially offering financial benefits to the patient and health care system.<sup>50</sup> The use of minimally invasive surgical techniques to expedite postoperative recovery with a decreased duration of hospital stay is yet another advantage that may contribute to overall cost savings.<sup>51,52</sup>

With our subgroup analysis of factors influencing patient dissatisfaction, we were able to determine a relationship between age, a revisional Nissen fundoplication, and intraoperative

estimated blood loss. Postoperative antireflux medication use at latest follow-up was also associated with an increased likelihood of patient dissatisfaction and patient-reported incidence of non-resolving chronic cough, suggesting advanced disease in this group. In addition, an abnormal Johnson-DeMeester score and the presence of cough on analysis of symptom association during preoperative ambulatory pH testing were not predictive of postoperative resolution of subjective chronic cough. These findings indicate that preoperative pH testing is not very sensitive in establishing a cause-and-effect relationship with cough symptoms. This surprisingly low sensitivity may be related to patient underreporting of cough during the 24-hour pH testing compared with other frequently reported symptoms like heartburn, regurgitation, and chest pain. When patients receive their instructions at the onset of their pH testing, it is conceivable that they receive more coaching on the logging of these common, classic symptoms rather than cough. Therefore, a thorough assessment of patients with chronic cough should not only rely on perioperative testing but also on clinical judgment and cough-specific QOL measures.

Our study has some important limitations. This series is representative of a single, high-volume foregut center with results that may not be broadly applicable to all surgeons or surgical centers that perform antireflux surgery. The possibility of recall bias is inherent to all studies that rely on any retrospective analysis. We attempted to diminish this by collecting all of our QOL surveys prospectively at predetermined time intervals. Another limitation was gradual patient loss to follow-up, which, although expected, may affect the analysis of longer-term outcomes.

In conclusion, patients with objective signs of GERD and objective signs of associated chronic cough demonstrate long-term benefit from LARS. Our study establishes that almost 8 in 10 patients experience complete resolution of symptoms at 3 years of follow-up and nearly three-fourths do not require PPI therapy after LARS. Robust operative volume, thorough and complete workup before operative therapy, and proper selection of patients with GERD-induced cough are paramount to achieving good outcomes.

### Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

### References

- Ford AC, Forman D, Moayyedi P, Morice AH. Cough in the community: A cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax*. 2006;61:975–979.
- Chamberlain SA, Garrod R, Douiri A, et al. The impact of chronic cough: A cross-sectional European survey. *Lung*. 2015;193:401–408.
- McGarvey LP, Carton C, Gamble LA, et al. Prevalence of psych morbidity among patients with chronic cough. *Cough*. 2006;2:4.
- Houghton LA, Lee AS, Badri H, DeVault KR, Smith JA. Respiratory disease and the oesophagus: Reflux, reflexes and microaspiration. *Nat Rev Gastroenterol Hepatol*. 2016;13:445–460.
- Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. *Cough*. 2013;9:12.
- Smith JA, Decalmer S, Kelsall A, et al. Acoustic cough-reflex associations in chronic cough: Potential triggers and mechanisms. *Gastroenterology*. 2010;139:754–762.
- El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: A systematic review. *Gut*. 2014;63:871–880.
- Moore M, Afaneh C, Benhuri D, Antonacci C, Abelson J, Zarnegar R. Gastroesophageal reflux disease: A review of surgical decision making. *World J Gastrointest Surg*. 2016;8:77–83.
- Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143:1179–1187.e3.
- Francis DO, Rymer JA, Slaughter JC, et al. High economic burden of caring for patients with suspected extraesophageal reflux. *Am J Gastroenterol*. 2013;108:905–911.
- Ali T, Roberts DN, Tierney WM. Long-term safety concerns with proton pump inhibitors. *Am J Med*. 2009;122:896–903.
- Kheloufi F, Frankel D, Kaspi E, et al. Chronic use of proton pump inhibitors, adverse events and potential biological mechanisms: A translational analysis. *Therapie*. 2018;73:273–281.
- Oelschlager BK, Quiroga E, Parra JD, Cahill M, Polissar N, Pellegrini CA. Long-term outcomes after laparoscopic antireflux surgery. *Am J Gastroenterol*. 2008;103:280–287. quiz 288.
- Gee DW, Andreoli MT, Rattner DW. Measuring the effectiveness of laparoscopic antireflux surgery: Long-term results. *Arch Surg*. 2008;143:482–487.
- Fein M, Bueter M, Thalheimer A, et al. Ten-year outcome of laparoscopic antireflux surgery. *J Gastrointest Surg*. 2008;12:1893–1899.
- Heidelbaugh JJ, Gill AS, Van Harrison R, Nostrant TT. Atypical presentations of gastroesophageal reflux disease. *Am Fam Physician*. 2008;78:483–488.
- Klingensmith ME, Aziz A, Bharat A, et al. *The Washington Manual of Surgery*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
- Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002;16:274–277.
- Stefanidis D, Hope W, Kohn G, Reardon P, Richardson W, Fanelli R. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc*. 2010;24:2647–2669.
- Weltz AS, Zahiri HR, Sibia US, Wu N, Fantry GT, Park AE. Patients are well served by Collis gastroplasty when indicated. *Surgery*. 2017;162:568–576.
- Park AE, Hoogerboord CM, Sutton E. Use of the falciform ligament flap for closure of the esophageal hiatus in giant paraesophageal hernia. *J Gastrointest Surg*. 2012;16:1417–1421.
- Velanovich V. The development of the GERD-HRQL symptom severity instrument. *Dis Esophagus*. 2007;20:130–134.
- Carrar RL, Khidr A, Gold KF, et al. Validation of a quality-of-life instrument for laryngopharyngeal reflux. *Arch Otolaryngol Head Neck Surg*. 2005;131:315–320.
- McHorney CA, Robbins J, Lomax K, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. *Dysphagia*. 2002;17:97–114.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
- French CL, Irwin RS, Curley FJ, Krikorian CJ. Impact of chronic cough on quality of life. *Arch Intern Med*. 1998;158:1657–1661.
- Stefanidis D, Hope WW, Kohn GP, et al. Guidelines for surgical treatment of gastroesophageal reflux disease. *Surg Endosc*. 2010;24:2647–2669.
- Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: A systematic review and meta-analysis. *Nephrol Dial Transplant*. 2018;33:331–342.
- Nagata N, Niikura R, Yamada A, et al. Acute middle gastrointestinal bleeding risk associated with NSAIDs, antithrombotic drugs, and PPIs: A multicenter case-control study. *PLoS One*. 2016;11:e0151332.
- Fujiwara Y, Watanabe T, Muraki M, et al. Association between chronic use of proton pump inhibitors and small-intestinal bacterial overgrowth assessed using lactulose hydrogen breath tests. *Hepatogastroenterology*. 2015;62:268–272.
- Jobe BA, Richter JE, Hoppo T, et al. Preoperative diagnostic workup before antireflux surgery: An evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. *J Am Coll Surg*. 2013;217:586–597.
- Yermilov I, McGory ML, Shekelle PW, Ko CY, Maggard MA. Appropriateness criteria for bariatric surgery: Beyond the NIH guidelines. *Obesity (Silver Spring)*. 2009;17:1521–1527.
- Fischella PM, Patti MG. GERD procedures: When and what? *J Gastrointest Surg*. 2014;18:2047–2053.
- Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg*. 1999;3:292–300.
- Carroll TL, Nahikian K, Asban A, Wiener D. Nissen fundoplication for laryngopharyngeal reflux after patient selection using dual pH, full column impedance testing: A pilot study. *Ann Otol Rhinol Laryngol*. 2016;125:722–728.
- Tatarian T, Pucci MJ, Palazzo F. A modern approach to the surgical treatment of gastroesophageal reflux disease. *J Laparoendosc Adv Surg Tech A*. 2016;26:174–179.
- Carrasquer A, Targarona EM, Marinello F, Batlle X, Trias M. Laparoscopic fundoplication results in the treatment of the non-gastrointestinal symptoms of gastroesophageal reflux [in Spanish]. *Cir Esp*. 2012;90:238–242.
- Kaufman JA, Houghland JE, Quiroga E, Cahill M, Pellegrini CA, Oelschlager BK. Long-term outcomes of laparoscopic antireflux surgery for gastroesophageal reflux disease (GERD)-related airway disorder. *Surg Endosc*. 2006;20:1824–1830.
- Iqbal M, Batch AJ, Moorthy K, Cooper BT, Spychal RT. Outcome of surgical fundoplication for extra-oesophageal symptoms of reflux. *Surg Endosc*. 2009;23:557–561.
- Ranson ME, Danielson A, Maxwell JG, Harris JA. Prospective study of laparoscopic nissen fundoplication in a community hospital and its effect on typical, atypical, and nonspecific gastrointestinal symptoms. *JSLs*. 2007;11:66–71.

41. Park JM, Kim BJ, Kim JG, Chi KC. Factors predicting outcomes of laparoscopic Nissen fundoplication for gastroesophageal reflux disease: Experience at a single institution in Korea. *Ann Surg Treat Res*. 2017;92:184–190.
42. Eid SM, Boueiz A, Paranj S, Mativo C, Landis R, Abougergi MS. Patterns and predictors of proton pump inhibitor overuse among academic and non-academic hospitalists. *Intern Med*. 2010;49:2561–2568.
43. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292:1955–1960.
44. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect*. 2003;54:243–245.
45. Arora P, Gupta A, Golzy M, et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. *BMC Nephrol*. 2016;17:112.
46. Andersen BN, Johansen PB, Abrahamson B. Proton pump inhibitors and osteoporosis. *Curr Opin Rheumatol*. 2016;28:420–425.
47. Batchelor R, Gilmartin JF, Kemp W, Hopper I, Liew D. Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review. *J Gastroenterol Hepatol*. 2017;32:1426–1435.
48. Pello Lazaro AM, Cristobal C, Franco-Pelaez JA, et al. Use of proton-pump inhibitors predicts heart failure and death in patients with coronary artery disease. *PLoS One*. 2017;12:e0169826.
49. Cookson R, Flood C, Koo B, Mahon D, Rhodes M. Short-term cost effectiveness and long-term cost analysis comparing laparoscopic Nissen fundoplication with proton-pump inhibitor maintenance for gastro-oesophageal reflux disease. *Br J Surg*. 2005;92:700–706.
50. Simorov A, Ranade A, Jones R, et al. Long-term patient outcomes after laparoscopic anti-reflux procedures. *J Gastrointest Surg*. 2014;18:157–162; discussion 162–163.
51. Ng R, Mullin EJ, Maddern GJ. Systematic review of day-case laparoscopic Nissen fundoplication. *ANZ J Surg*. 2005;75:160–164.
52. Narain PK, Moss JM, DeMaria EJ. Feasibility of 23-hour hospitalization after laparoscopic fundoplication. *J Laparoendosc Adv Surg Tech A*. 2000;10:5–11.

*Surgery* is abstracted and/or indexed in *Index Medicus*, *Science Citation Index*, *Current Contents/Clinical Medicine*, *Current Contents/Life Sciences*, and MEDLINE.

This Journal has been registered with Copyright Clearance Center, Inc, 222 Rosewood Dr, Danvers, MA 01923. Consent is given for the copying of articles for personal or internal use of specific clients. This consent is given on the condition that the copier pay directly to the Center the per-copy fee stated on the first page of each article for copying beyond that permitted by US Copyright Law. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works. All inquiries regarding copyrighted material from this publication other than those that can be handled through Copyright Clearance Center should be directed to Journals Permission Department, Elsevier Inc, 3521 Riverport Lane, Maryland Heights, MO 63043; (314) 447-8871