Retrospective Cohort Study

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Exploring objective factors to predict successful outcomes after laparoscopic Nissen fundoplication

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Background: Currently, the reported parameters that predict the resolution of symptoms after surgery are largely subjective and unreliable. Considering that fundoplication rebuilds the structural integrity of the lower esophageal sphincter (LES), the authors focused on searching for objective and quantitative predictors for the resolution of symptoms based on the anatomical issues and whether an antireflux barrier can be well established or not.

Materials and methods: The authors reviewed the prospectively collected data of 266 patients with gastroesophageal reflux disease (GERD) who had undergone laparoscopic Nissen fundoplication (LNF). All patients were diagnosed with GERD using preoperative esophagogastroduodenoscopy, 24-h ambulatory esophageal pH monitoring, and high-resolution esophageal manometry. The patients received GERD symptom surveys using the validated Korean Antireflux Surgery Group questionnaire twice: preoperatively and 3 months after the surgery.

Results: After excluding patients with insufficient follow-up data, 152 patients were included in the analysis. Multivariate logistic regression analyses revealed that a longer length of the LES and lower BMI determined better resolution of typical symptoms after LNF (all $P < 0.05$). Regarding atypical symptoms, higher resting pressure of LES and DeMeester score greater than or equal to 14.7 were associated with better resolution after the surgery (all $P < 0.05$). After LNF, typical symptoms improved in 34 out of 37 patients (91.9%) with a length of LES > greater than .05 cm, BMI less than 23.67 kg/m^2, and atypical symptoms were resolved in 16 out of 19 patients (84.2%) with resting pressure of LES greater than or equal to 19.65 mm Hg, DeMeester score greater than or equal to 14.7.

Conclusion: These results show that the preoperative length and resting pressure of LES is important in the objective prediction of symptom improvement after LNF.

Keywords: gastroesophageal reflux disease, high-resolution esophageal manometry, laparoscopic fundoplication, lower esophageal sphincter

Introduction

Laparoscopic Nissen fundoplication (LNF) is currently considered an effective surgical treatment option for gastroesophageal reflux disease (GERD). In patients with reflux symptoms refractory to medical treatments, fundoplication is an effective alternative to medical treatments[1] considering its high success rate, ranging from 80 to 90%[2], and its cost-effectiveness when compared to long-term medical treatments[3]. Nevertheless,

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Currently, there are no reported metrics of any kind which are objectively associated with the outcome of the fundoplication surgery. However, this multicenter study shows that the total length and resting pressure of the lower esophageal sphincter can strongly predict the resolution of GERD symptoms after laparoscopic Nissen fundoplication.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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~10% of the patients still report ongoing symptoms or recurrence after the surgery[4].

For decades, numerous attempts have been made to identify objective clinical parameters to accurately predict the prognosis of LNF. The severity or specific manifestations of preoperative symptoms, response to proton pump inhibitors (PPIs), medical treatment options, and abnormal acidic reflux seen in 24-h pH monitoring were once suggested as powerful predictors for the resolution of symptoms after the surgery[5–8]. However, their usefulness as predictors, varied according to the literature, probably because these factors highly depend on the baseline characteristics of each patient[9]. Especially, 24-h pH monitoring could not reliably predict the outcome due to the large variance of their results. Although the additional use of impedance parameters has enabled the detection of nonacid reflux and increased the number of positive symptom indices, it is still uncertain whether such increased detection of nonacid reflux can contribute to better prediction of postoperative outcomes[10].

Considering that fundoplication recreates an elongated tunnel barrier holding higher pressures to suppress reflux, the process of searching for objective and quantitative predictors of symptom resolution should focus on the structural anatomy of whether an antireflux barrier can be well established after surgery. High-resolution esophageal manometry (HRM) is a clinical device that can measure the pressure changes at equidistant points along the esophagus, producing a topographic plot that can assess the functional motility of the esophagus[11]. As such, HRM was used mainly to rule out contraindications of LNF such as achalasia, but its utility as a predictive tool for prognosis has not been studied. Since pathological esophageal acid exposure has been reported to be associated with the reduced intra-abdominal length and resting pressure of the LES, topographic information of the LES provided by HRM findings might provide useful information for predicting the resolution of GERD symptoms after Nissen fundoplication[12].

Herein, we aimed to identify novel, objective, and quantitative measurement parameters that can accurately predict the resolution of reflux symptoms after fundoplication by analyzing prospectively collected multi-institutional cohorts, including HRM findings.

HIGHLIGHTS

- Longer length (>4.05 cm) of the lower esophageal sphincter and lower BMI (<23.67 kg/m^2) determined better resolution in typical symptoms of gastroesophageal reflux disease after laparoscopic Nissen fundoplication.
- Higher resting pressure (≥19.65 mm Hg) of lower esophageal sphincter and DeMeester score greater than or equal to 14.7 were associated with better resolution in atypical symptoms of gastroesophageal reflux disease after antireflux surgery.
- Our derived quantitative parameters can be suggested as objective tools to predict the improvement of symptoms after antireflux surgery.

Material and methods

Study design and cohorts

We have followed the STROCSS 2019 guideline for this study[13], Supplemental Digital Content 1, http://links.lww.com/JS9/A249. We reviewed a prospectively collected database of consecutive patients who underwent LNF for GERD from October 2012 to October 2020 at two tertiary teaching hospitals in the Republic of Korea. The antireflux surgery was performed according to the guidelines stated in European Association of Endoscopic Surgery, Society of American Gastrointestinal and Endoscopic Surgeons[14], and Journal of Gastric Cancer[14–16]. We primarily performed LNF for GERD patients who have expectations of long-term efficacy of surgery with fear for lifelong time medical treatment and its complications. Then, we selectively performed the surgery for patients who suffered from atypical symptoms, after excluding other underlying disease that can provoke extraesophageal symptoms[17]. The inclusion criteria were as follows: age greater than or equal to 20 years; patients who underwent LNF for GERD; duration of follow-up greater than or equal to 3 months; and definitively diagnosed with GERD before surgery. According to the American Journal of Gastroenterology guideline, GERD was diagnosed by preoperative symptom survey, esophagogastroduodenoscopy (EGD), 24-h intraluminal ambulatory pH monitoring, and HRM[18]. Patients with severe (type IV, protrusion of the stomach and other abdominal organs through the esophageal hiatus) hiatal hernia, esophageal achalasia, or any history of prior antireflux surgeries were excluded. This study was approved by the institutional review board of each participating institution, including the Korea University Medical Center (No.2020AN0270). Informed consent to be included in the study or equivalent was obtained from all the patients.

GERD evaluation

EGD and esophageal 24-h intraluminal ambulatory pH monitoring were performed to diagnose and evaluate GERD. EGD was performed to diagnose GERD by validating reflux esophagitis, checking the existence of hiatal hernia, and ruling out other conditions. The extent of esophagitis was evaluated with respect to the Los Angeles classification[19]. Meanwhile, esophageal 24-hintraluminal ambulatory pH monitoring was performed before the surgery to confirm the indication of fundoplication and monitor the modality of the reflux. A catheter sensor was placed 5 cm above the proximal border of the LES. Each reflux was considered acidic when the pH of the refluxate was less than 4. Each acid reflux composite score (DeMeester score) was calculated using the following values: percentage of total time in reflux, percentage of time in reflux in the upright position, percentage of time in reflux in the supine position, the total number of reflux episodes, number of reflux episodes continuing over 5 min, and longest duration of reflux among all reflux episodes. DeMeester scores greater than 14.7 were considered abnormal acid reflux[20].

HRM was performed preoperatively, assessing the patients' esophageal motility and measuring the LES's structural values and competence-related characteristics[21]. Also, 10 consecutive liquid swallows were performed by tested patients to exclude hypercontractility, which indicates esophageal achalasia, contraindicating antireflux surgery. Using Zvu v2.1, an automatic numerical analysis software that provides a topographic pressure contour plot of the HRM, the following factors were measured: the length of the esophagus was defined as the distance between the two high-pressure zones [the upper and lower esophageal

sphincters (LESs)]; the total length of the LES was defined as the total distance between two proximal and distal LES locations; the distal location was defined as the average value of the proximal and distal LES locations, and the resting pressure was defined as the basal pressure at the esophagogastric junction during mid-respiration.

For symptomatic GERD assessment, the patients were asked to fill out the validated questionnaire developed by the Korean Antireflux Surgery Group: a week before the surgery and 3 months after the surgery[22]. The Korean Antireflux Surgery Group questionnaire consists of a visual analog scale from 0 (no symptoms) to 10 (very severe), assessing the severity and frequency of each type (heartburn, regurgitation, epigastric pain) and atypical (globus sensation, throat pain, hoarseness, chronic cough, sputum, bronchial asthma, recurrent otitis, recurrent rhinitis, noncardiac chest pain) symptom before the surgery, and Visick score from I (absolute satisfaction with complete remission) to V (worsening of symptoms) assessing the extent of the resolution regarding each typical and atypical symptom after the surgery. A patient was considered to have either typical or atypical symptoms before the surgery if (1) the patient had at least two manifestations from each symptom category with a visual analog scale greater than 5 and (2) the patient suffered from the symptoms at least every week. Only patients who answered with a Visick I score after surgery were defined as having complete resolution of typical and atypical symptoms[23].

Surgical procedure

At each institution, LNF was performed by two surgeons specializing in foregut surgery. If present, a hiatal hernia repair was also performed. The fundoplication was made with two- or three-point nonabsorbable sutures with an adequate length of 1.5 cm, and a shoeshine maneuver was performed to ensure anatomical redundancy to prevent postoperative dysphagia. Additional suture fixations were made between the fundoplication wrap and distal esophagus, along with the crural repair site, to avoid postoperative thoracic migration. No surgical complications related to blood loss or damage to the vagus nerve were observed.

Statistical analyses

Statistical tests for continuous variables were performed using the *t*-test or Mann–Whitney *U*-test and Fisher's exact test for discrete variables. Univariate logistic analysis was performed to select potential predicting factors for resolution of symptoms after antireflux surgery. Then, multivariate logistic regression using backward stepwise selection was performed to find the most independent factors predicting the resolution of symptoms after antireflux surgery. In backward stepwise selection approach, variables with the highest *P* value were gradually eliminated from the regression model at each step to find a reduced model that best explains the data. The receiver operator characteristic (ROC) curve was plotted for each predictor with continuous variables, and Youden's *J* statistics were calculated to find the optimal cutoff values[24]. Finally, the efficacy of the calculated predictors was validated by comparing the difference in the resolution of symptoms between subgroups divided by these cutoff points. Two-sided *P* values less than 0.05 was considered statistically significant. The statistical software used for this study was R [version 4.2.1 (R Core Team (2022). R: Language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/] and the pROC package[25] were used to analyze the ROC curves.

Results

From October 2012 to October 2020, 266 patients diagnosed with GERD underwent LNF at the two tertiary teaching hospitals in the Republic of Korea. We excluded 114 patients who were missed during the follow-up period, and the remaining 152 patients were included in our analysis. The characteristics of the study participants are summarized in Table 1. The mean age of the cohorts was 48.3 ± 17.2 years, with 49.3% (*N* = 75) being men and 50.7% (*N* = 77) women. The mean BMI was 23.1 ± 3.6 kg/m^2. Regurgitation (74%), globus sensation (74%), and heartburn (63%) were the most common symptoms reported

Table 1

Patient's baseline characteristics.

Variables	Mean (SD), median (interquartile range) (*N* = 152)
Age, years	48.3 (17.2)
Sex, male : female [*n* (%)]	75 (49.3) : 77 (50.7)
BMI, kg/m^2	23.1 (3.6)
Preoperative symptoms (*N* = 137) [*n* (%)]	
Typical	
Overall	124 (90.5)
Epigastric pain	42 (31)
Heartburn	86 (63)
Regurgitation	101 (74)
Atypical [*n* (%)]	
Overall	111 (81.0)
Bronchial asthma	4 (2.9)
Chronic cough	40 (29)
Globus sensation	100 (74)
Hoarseness	37 (27)
Noncardiac chest pain	7 (5.1)
Recurrent otitis	10 (7.4)
Recurrent rhinitis	6 (4.4)
Sputum	13 (9.6)
Throat pain	49 (36)
Duration of GERD symptoms, months	48 (24–120)
Usage period of proton pump inhibitor, months	15 (6–48)
Response to proton pump inhibitor before surgery (*N* = 133) [*n* (%)]	
None	32 (24.0)
Fair	88 (66.2)
Excellent	13 (9.8)
Reflux esophagitis detected by preoperative endoscopy (*N* = 142) [*n* (%)]	
None	72 (50.7)
Los Angeles classification grade A, B	67 (47.2)
Los Angeles classification grade C, D	3 (2.1)
Hiatal hernia (*N* = 142) [*n* (%)]	57 (40.1)
DeMeester score	10.0 (3.9–30.4)
High-resolution manometry metrics	
Lower esophageal sphincter	
Total length, cm	4.1 (3.0–5.1)
Resting pressure, mm Hg	20 (14–30)
Upper esophageal sphincter	
Total length, cm	4.0 (3.0–5.3)
Resting pressure, mm Hg	58 (32–101)

GERD, gastroesophageal reflux disease.

before surgery. The median duration of GERD symptoms was 48 months [interquartile range (IQR): 24–120], and 101 out of 133 (75.9%) patients had a prior response to PPI medication. Preoperative endoscopic findings detected high-grade erosive esophagitis (grades C and D) in three (2.1%) patients. Abnormal pH metric (DeMeester score > 14.7) was observed in 74 (53.2%) patients. The total length, resting pressure, and integrated residual pressure of the LES were 4.10 (IQR: 3.00–5.07) cm, 20.0 (IQR: 14.2–30.0) mm Hg, and 7.5 (IQR: 4.25–13.00) mm Hg, respectively. After the surgery, 99 (79.8%) of 124 and 76 (68.5%) of 111 patients reported resolution of typical and atypical symptoms, respectively. The detailed resolution of each individual symptoms was described in Table 2. Thirty-three patients (21.7%) had postoperative complications such as dysphagia (11.2%), inability to belch (7.2%), gas bloat (15.8%), and flatulence (17.8%) (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A250).

Since this study was originally intended to find reliable quantitative parameters to predict the resolution of symptoms after antireflux surgery, we conducted a logistic regression analysis for the variables to determine the improvement of symptoms. Multivariate analysis revealed that the total length of the LES [odds ratio (OR) = 2.100, CI = 1.452–3.036, $P < 0.001$] and BMI (OR = 0.853, CI = 0.737–0.987, $P = 0.032$) were independent clinical parameters for predicting the resolution of typical symptoms after LNF (Table 3). In terms of anticipating the improvement of atypical symptoms, the higher resting pressure of LES (OR = 1.066, CI = 1.012–1.122, $P = 0.016$) and DeMeester score of greater than 14.7 (OR = 3.197, CI = 1.069–9.563, $P = 0.038$) were found to be independent predictive parameters (Table 4). The distribution of patients whose reflux symptoms were resolved or unresolved according to the total length of the LES and resting pressure of the LES before fundoplication is plotted in Figure 1.

Except for the DeMeester score cutoff of 14.7, ROC curve analyses were performed for calculated predictors with continuous variables, and the optimal cutoff points were as follows: the total length of the LES (4.05 cm), BMI (23.67 kg/m^2), and resting pressure of the LES (19.65 mmHg) (Figure 2). Based on these cutoff points, the patients after completing outpatient clinic follow-up, were subdivided into four groups. Regarding the typical symptom, the group with a length greater than 4.05 cm and BMI less than 23.67 kg/m^2 achieved the highest percentage of resolution (34/37, 91.9%) after LNF (Table 5). In terms of the extraesophageal symptoms, the patients with a pressure of LES greater than 19.65 mm Hg and a DeMeester score greater than 14.7 experienced the most favorable outcomes (16 out of 19, 84.2%) (Table 6).

Table 2

Postoperative resolution of typical and atypical symptoms.

Variables	Patients with resolution (*N*)/patients with preoperative symptom (*N*), (%)
Typical symptoms	
Overall (*N* = 124)	99/124 (79.8)
Epigastric pain (*N* = 42)	32/42 (76.2)
Heartburn (*N* = 86)	68/86 (79.1)
Regurgitation (*N* = 101)	84/101 (83.2)
Atypical symptoms	
Overall (*N* = 111)	76/111 (68.5)
Bronchial asthma (*N* = 4)	3/4 (75.0)
Chronic cough (*N* = 40)	25/40 (62.5)
Globus sensation (*N* = 100)	52/100 (52.0)
Hoarseness (*N* = 37)	21/37 (56.8)
Noncardiac chest pain (*N* = 7)	4/7 (57.1)
Recurrent otitis (*N* = 10)	7/10 (70.0)
Recurrent rhinitis (*N* = 6)	4/6 (66.7)
Sputum (*N* = 13)	7/13 (53.8)
Throat pain (*N* = 49)	30/49 (61.2)

Discussion

Appropriate selection of candidates for antireflux surgery is critical for successful outcomes. Therefore, surgeons have sought to identify objective and quantitative parameters that can predict symptom remission after LNF. The primary purpose of the LNF procedure is to produce a wrap around the lower portion of the esophagus, thereby reinforcing the pressure zone of the antireflux barrier with incompetent LES[26]. In light of this fundamental principle, we first attempted to search for objectively measurable variables related to the topographic structural information of the LES itself. At the same time, previous studies have only focused on subjective or inconsistent metrics such as the patient's response to PPI medication, pH monitoring score, and preoperative symptom surveys. In the current era, GERD is no longer a disease limited to the western population but a nationwide clinical issue affecting all susceptible individuals, especially in East Asia and the Pacific[27]. Also, in this perspective, the prospectively collected clinical data from the two tertiary teaching hospitals, which currently perform the largest cases of LNF in Korea by highly experienced surgeons, can provide coherence and liableness to our study.

Theoretically, as the newly established barrier by wrapping lengthens vertically and the thoracoabdominal pressure gradient decreases, the antireflux competence of fundoplication is expected to be maximized[28]. For these reasons, antireflux surgery in the early era focused on increasing the length of wrapping, but the length of wrapping has been gradually shortened to reduce persistent dysphagia caused by overly long fundoplication[28,29]. Considering that the length of wrapping is usually standardized as 1–2 cm (formerly 3–5 cm) these days, providing additional pressurization to the already existing pressure zone is the key to such successful modification[30]. In this situation, the original length of LES is more important for symptom resolution than the reflux-preventing tunnel artificially lengthened through fundoplication, and a longer length of LES is inevitably more advantageous than a shorter one. Interestingly, our study also showed that a longer LES (especially > 4.05 cm) and a patient's lower BMI independently predicted the resolution of typical GERD symptoms after LNF. These findings are supported by previous studies showing that antireflux competence is positively correlated with the original length of LES[31], and the fundoplication procedure increased the original length of LES itself[32]. To further reinforce the validity of these results, future large-scale clinical trials are required to estimate the changes in the length of LES after antireflux surgery through HRM findings.

Cowgill *et al.*[33] and Riedl *et al.*[34] have proposed that preoperative HRM parameters regarding the length and pressure of LES cannot predict the fundoplication outcome. In their methods, they explicitly categorized the HRM parameters as indicating the

Table 3

Univariate and multivariate logistic regression analyses for the clinical variables predicting the resolution of typical symptoms after laparoscopic Nissen fundoplication.

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Male (vs. female)	1.162 (0.641–2.102)	0.619		
Age, years (per increase)	0.993 (0.976–1.010)	0.424		
BMI, kg/m^2 (per increase)	0.884 (0.808–0.962)	**0.005***	0.853 (0.737–0.987)	**0.032**
Response to PPI				
None	1.000			
Fair	2.609 (1.258–5.447)	**0.010**		
Excellent	5.727 (1.640–27.05)	**0.012**		
24-h ambulatory pH monitoring				
DeMeester score	0.995 (0.983–1.006)	0.316		
DeMeester score > 14.7	0.952 (0.397–2.289)	0.912		
High-resolution manometry metrics				
Length of the esophagus	1.263 (0.971–1.710)	0.097		
Lower esophageal sphincter				
Total length, cm	2.149 (1.536–3.167)	< **0.001**	2.100 (1.452–3.036)	< **0.001**
Resting pressure, mm Hg	1.045 (1.010–1.088)	**0.018**		
Integrated relaxation pressure, mm Hg	0.990 (0.877–1.065)	0.788		
Distal location, cm	1.157 (1.024–1.323)	**0.024**		
Upper esophageal sphincter				
Total length, cm	1.339 (1.013–1.836)	0.052		
Resting pressure, mm Hg	1.001 (0.994–1.008)	0.805		
Distal location, cm	0.999 (0.911–1.122)	0.977		

OR, odds ratio; PPI, proton pump inhibitor.
*P value < 0.05.

patient's LES as 'normal' or 'incompetent' if the LES pressure was below 8–10 mm Hg and/or the LES length was below 2 cm. However, we conducted logistic regression analyses with HRM variables considering the variables as continuous variables, and most importantly, the optimal cutoff point was shown to be 4.050 cm for the LES length. Therefore, we assert that our study does not disagree with, but rather encompasses, their findings due to the largely different categorization values.

After fundoplication by wrapping, newly created pressure zone of patients with longer LES makes it harder for refluxates to reach

Table 4

Univariate and multivariate logistic regression analyses for the clinical variables predicting the resolution of atypical symptoms after laparoscopic Nissen fundoplication.

Variables	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Male (vs. female)	0.858 (0.459–1.603)	0.632		
Age, years (per increase)	1.008 (0.990–1.027)	0.391		
BMI, kg/m^2 (per increase)	0.912 (0.831–0.997)	**0.046***		
Response to PPI				
None	1.000			
Fair	1.769 (0.803–4.019)	0.162		
Excellent	4.231 (1.162–18.08)	**0.036**		
24-h ambulatory pH monitoring				
DeMeester score	1.011 (0.997–1.031)	0.192		
DeMeester score > 14.7	2.734 (1.076–7.221)	**0.037**	3.197 (1.069–9.563)	**0.038**
High-resolution manometry metrics				
Length of the esophagus	1.178 (0.898–1.585)	0.246		
Lower esophageal sphincter				
Total length, cm	1.162 (0.883–1.553)	0.293		
Resting pressure, mm Hg	1.063 (1.022–1.111)	**0.004**	1.066 (1.012–1.122)	**0.016**
Integrated relaxation pressure, mm Hg	1.181 (0.922–1.628)	0.224		
Distal location, cm	1.050 (0.923–1.200)	0.463		
Upper esophageal sphincter				
Total length, cm	0.987 (0.759–1.283)	0.921		
Resting pressure, mm Hg	0.999 (0.991–1.006)	0.729		
Distal location, cm	0.874 (0.715–1.053)	0.169		

OR, odds ratio; PPI, proton pump inhibitor.
*P value < 0.05.

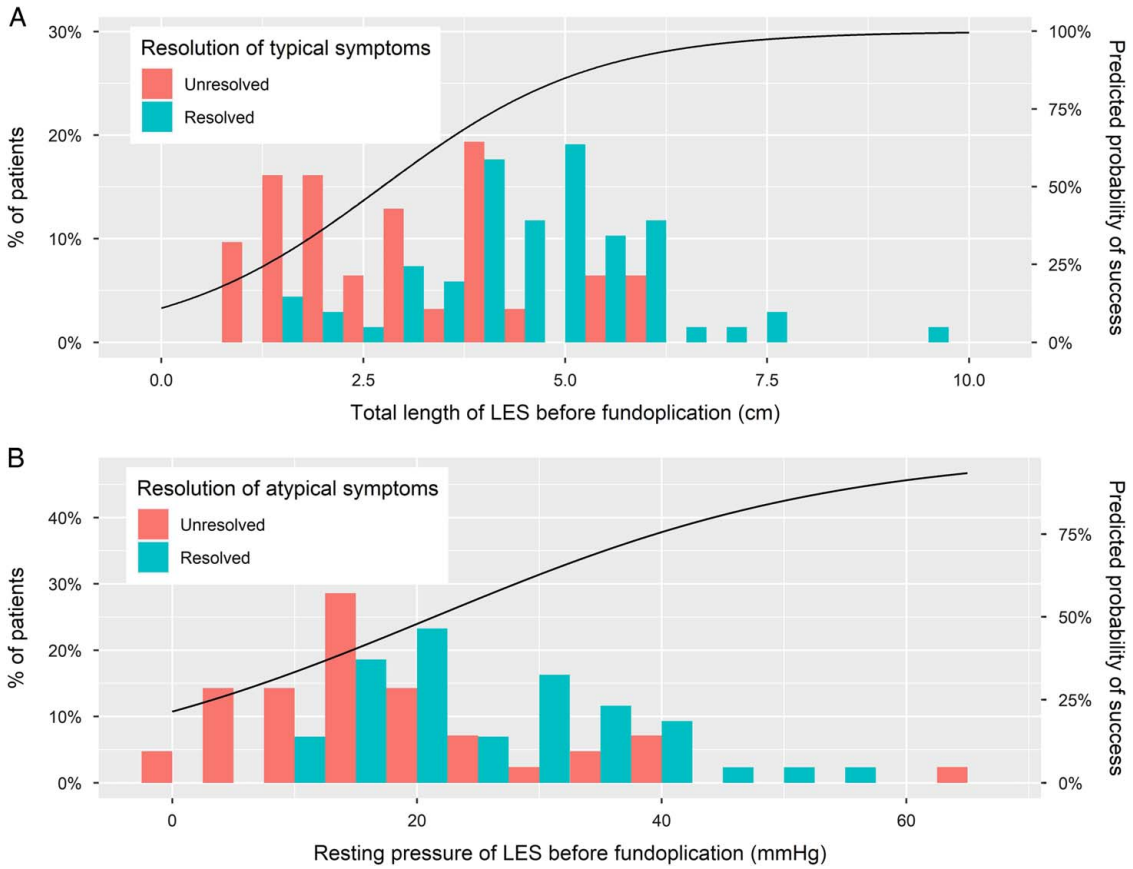

Figure 1. Distribution of (A) the total length of lower esophageal sphincter (LES) and (B) the resting pressure of LES before fundoplication with their logistic regression curves.

distal esophagus than those of patients with shorter one. For successful prevention of reflux, the reflux force generated by patients' intragastric pressure should not be so great as to counteract the suppression power of the newly created barrier with the advantage of longer LES. In the current study, along with the longer length of the LES, the patient's lower BMI also independently determined the resolution of typical symptoms after surgery. Obesity has long been known to be the main cause of GERD[35], inducing increased intragastric pressure, producing a constant strain on the antireflux barrier in obese patients compared to normal individuals[36]. When surgeons consider bariatric and metabolic surgery in obese patients with GERD symptoms, they usually prefer Roux-en-Y gastric bypass to sleeve gastrectomy to alleviate the effects of increased intragastric

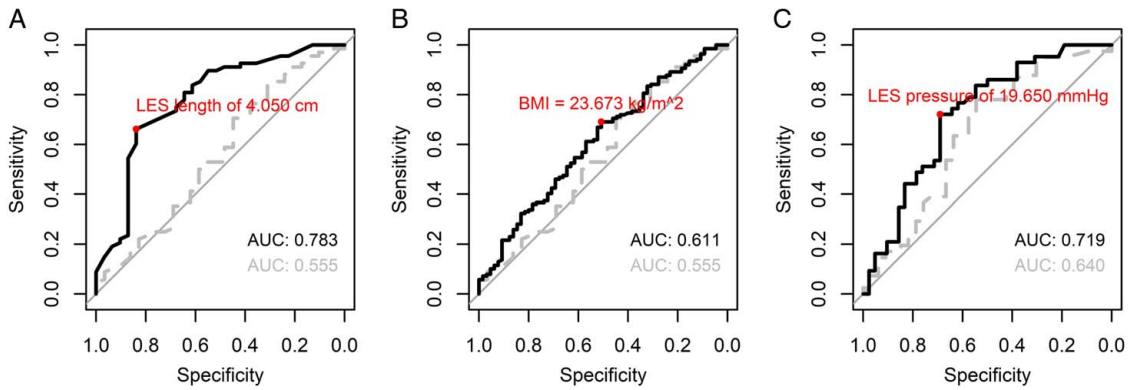

Figure 2. Receiver operator characteristic curves for the continuous variables predicting resolution of symptoms by (A) length of lower esophageal sphincter (LES), compared to the DeMeester score, (B) BMI (kg/m^2), compared to the DeMeester score, and (C) pressure of lower esophageal sphincter (mm Hg), compared to the DeMeester score. AUC, area under the curve.

Table 5

Subgroup analysis for the resolution of typical symptoms based on predicting parameters.

Patient subgroups divided by the predictors of typical symptoms	Resolution of typical symptoms [*n*/*N* (%)]*
Length of lower esophageal sphincter <4.05 cm, BMI < 23.67 kg/m^2	16/30 (53.3)
Length of lower esophageal sphincter ≥4.05 cm, BMI < 23.67 kg/m^2	34/37 (91.9)
Length of lower esophageal sphincter <4.05 cm, BMI ≥23.67 kg/m^2	7/19 (36.8)
Length of lower esophageal sphincter ≥4.05 cm, BMI ≥23.67 kg/m^2	11/13 (84.6)

*Fisher's exact test was performed, and the resolution ratios of four groups were significantly different from each other ($P < 0.001$).

pressure[37]. However, obesity is a modifiable disease that partially explains its independent predictability compared to the factor of LES length and further suggests that noninvasive weight loss programs could be recommended to patients who are awaiting resolution of typical symptoms after fundoplication, as weight loss alone has already been shown to significantly reduce GERD symptoms[38]. We present a BMI of less than 23.67 kg/m^2 as an optimal target for obese patients who want to expect an improvement of GERD symptoms through weight loss. Since the cutoff value for defining obesity is lower in Asian populations and Koreans, and the cohort of this study consisted of Korean patients with GERD, the BMI cutoff point determining the resolution of typical symptoms after LNF would be lower than that of the Western population[39,40].

Atypical symptoms, such as extraesophageal manifestation like chronic cough, asthma, bronchitis, and noncardiac chest pain, are extremely common and may occur completely unrelated to GERD. For these patients, if antireflux surgery is offered without fundamental treatment for respiratory or cardiovascular diseases, atypical symptoms will not resolve. Therefore, careful patient selection for truly confirmed GERD is important in anticipating the improvement of atypical symptoms. Our study revealed that a DeMeester score of greater than or equal to 14.7 predicted the resolution of atypical symptoms after LNF. This means that patients with truly confirmed GERD are better at improving atypical symptoms than those who may not have actual GERD. This can be strongly supported by the fact that the resolution of GERD-related respiratory symptoms could be predicted only by the presence of abnormal acid exposure (pH <4.0, DeMeester score ≥14.7) in the pharynx as determined by 24-h pH monitoring[41]. The pathophysiology of extraesophageal symptoms caused by truly confirmed GERD could also be explained as follows: first, when a mixture of both gastric (acid and pepsin) and duodenal (bile acids and pancreatic enzyme trypsin) content is exposed to the distal esophagus above the LES, it can directly contact the pharyngeal mucosa and lead to mucosal damage or irritations in the respiratory tract[42,43]. Especially, refluxate with acidic contents can more induce respiratory symptoms such as chronic chough, asthma[44–46]. Direct pharyngeal or laryngeal stimulation and aspiration cause a tracheal or bronchial cough response[47]. Second, acidification of the distal esophagus can stimulate acid-sensitive receptors, resulting in noncardiac chest pain[48]. In the distal esophagus, a vagally-mediated tracheal-bronchial reflex can also produce a cough[49]. The DeMeester score reflects the sum of acid exposure, total number, and duration of reflux episodes. Considering that acid exposure, and direct pharyngeal, laryngeal, or distal esophageal stimulations mainly provoke atypical symptoms, our results that a DeMeester score greater than 14.7 can predict resolution of atypical symptoms might be reasonable. Complete symptom control rates for typical and atypical symptoms were reported as 86.3 and 63.3%, respectively[22]. This means that even if patients (86.3%) who showed resolution from typical symptoms were diagnosed with true GERD, some of them (23%) might have extraesophageal symptoms that are not related to GERD itself. To improve extraesophageal symptoms through antireflux surgery, it is necessary to check whether atypical symptoms originate from GERD or fundamental underlying morbidities, as well as carefully select patients with truly confirmed GERD.

Recent studies have reported a causal relationship between lower resting pressure of LES and the underlying mechanism of generating respiratory symptoms in GERD patients. The hypopressure of LES, excessive transient LES relaxation has higher chances for gastric contents directly regurgitate from the distal esophagus to the proximal esophagus. Direct pharyngeal or laryngeal stimulation aggravated by reduced pressure of LES causes a tracheal or bronchial cough response. Cough can be also produced by a vagally-mediated tracheal-bronchial reflex in distal esophagus. In addition, gastric contents directly regurgitated from the distal to the proximal esophagus can form a spray. The spray then induces microaspirations into the upper respiratory tract, resulting in irritating symptoms such as cough, expectoration, and asthma[50,51]. A good example of hypopressure or excessive relaxation of LES is hiatal hernia, which is frequently observed in GERD patients. Patients with hiatal hernia have a high prevalence of concomitant laryngopharyngeal reflux symptoms since the LES is positioned proximally away from the crural diaphragm by which it maintains its pressure[52]. Our study also successfully confirmed that LES resting pressure of at least greater than or equal to 19.65 mmHg is necessary to expect the improvement of atypical symptoms after surgery. Of course, excessive pressure can lead to postoperative dysphagia, as

Table 6

Subgroup analysis for the resolution of atypical symptoms based on predictive parameters.

Patient subgroups divided by the predictors of atypical symptoms	Resolution of atypical symptoms [*n*/*N* (%)*]
Pressure of lower esophageal sphincter <19.65 mm Hg, DeMeester score <14.7	2/13 (15.4)
Pressure of lower esophageal sphincter ≥19.65 mm Hg, DeMeester score <14.7	12/19 (63.2)
Pressure of lower esophageal sphincter <19.65 mm Hg, DeMeester score ≥14.7	6/14 (42.9)
Pressure of lower esophageal sphincter ≥19.65 mm Hg, DeMeester score ≥14.7	16/19 (84.2)

*Fisher's exact test was performed, and the resolution ratios of four groups were significantly different from each other ($P < 0.001$).

revealed in other studies[53,54], but the pressure cutoff point was much lower in our results, suggesting that it should not be too low as well, either[55].

Our study has some limitations. First, the cohort of current study comprises of patients with short-term follow-up period and the data regarding postoperative 24-h pH monitoring or HRM are lacking. From 2012 to 2018, the two institutions performed 64.4% of antireflux surgeries in Korea (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A250)[27]. Despite the recommendation of medical staffs, it was not easy for some patients living far from the institutions to visit outpatient clinics and to pay for expensive cost of postoperative tests, long time after surgery. However, one study reported that patients who had resolution at 3 months remained to have a good response at 1-year after surgery[27]. Besides, GERD patients after surgery still had a lower rate of transient LES relaxations than medically treated patients for more than 5 years[56]. Second, we could not analyze the results after Dor or Toupet fundoplication. The surgeons in this study were more familiar with Nissen and believed that its antireflux effect would be greater than that of other types of antireflux surgery. Recent trends shifted from Nissen to Dor or Toupet fundoplication, which might be the better surgical approach for GERD with less postoperative complications such as dysphagia, bloating, and equal effectiveness as Nissen[57–59]. Third, participants in this study were young and well-improved by PPI medications. Generally, patients with well-responder to PPI had a better prognosis after fundoplication[14–16]. Although, PPI can buffer the acidity of refluxate, it cannot block the bolus exposure itself or nonacid exposure. Antireflux surgery has shown high efficacy in improving respiratory symptoms related to GERD, when compared to medical therapy[17]. Besides, we selectively perform LNF for patients who want to lead an active social life by freeing them from the burden of continuing medicines and its complications. Considering these, antireflux surgery can be a good treatment option for young GERD patients who responds well to PPI treatment. Fourth, discovered predicting factors might not directly deliver therapeutic effects. However, some of them can be modifiable and help patients preparing for successful antireflux surgery. For example, GERD patients can be recommended to have weight loss less than BMI 23.67 kg/m^2. And surgeons can suggest their patients to modify diet style not to decrease resting pressure of LES. Delayed gastric emptying can reduce the LES pressure and hinder the resolution of symptoms after antireflux surgery[60]. Interestingly, fatty foods impede gastric emptying and decrease LES pressure[61]. Alcohol and chocolate intake also weaken LES pressure, ultimately aggravating esophageal reflux[62,63]. Taken these together, future well-designed study is expected to resolve these issues in near future.

Conclusion

For patients who expect an improvement of typical symptoms after antireflux surgery, a longer length of LES (especially >4.05 cm) and lower BMI (especially <23.67 kg/m^2) can be quantitative predictive indices for favorable outcomes. Regarding atypical symptoms, higher resting pressure of LES (≥ 19.65 mmHg) and DeMeester score greater than or equal to 14.7 can predict better resolution after surgery. We hope that these quantitative parameters will be helpful to surgeons who want to objectively predict the improvement in typical and atypical symptoms after antireflux surgery.

Ethical approval

All procedures were performed in accordance with the ethical standards of the Responsible Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the institutional review board of Korea University Medical Center (No.2020AN0270). The requirement for written consent was waived by the IRB because of the retrospective nature of this study.

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Author contribution

Sangjun P. and S.-H.P. contributed equally to this work and should be considered first coauthors. Drs Sungsoo P. and J.-M.P. contributed equally to this work and should be considered corresponding coauthors and contributed in administrative, technical, and material support. Sangjun P., S.-H.P., and K.-S.Y.: statistical analyses. Sangjun P., S.-H.P.: drafting. acquisition, analysis, and interpretation of the clinical data; critical revision of the manuscript for important intellectual content; and supervision done by all authors.

Conflicts of interest disclosure

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Guarantor

The Guarantor, Sungsoo Park accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Availability of data and materials

The data sets generated and/or analyzed for this study are not publicly available according to the private information law but are available from the corresponding authors upon reasonable request.

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