JAMA | Original Investigation

Association Between Laparoscopic Antireflux Surgery and Recurrence of Gastroesophageal Reflux

John Maret-Ouda, MD; Karl Wahlin, MSc, PhD; Hashem B. El-Serag, MD, MPH; Jesper Lagergren, MD, PhD

IMPORTANCE Cohort studies, mainly based on questionnaires and interviews, have reported high rates of reflux recurrence after antireflux surgery, which may have contributed to a decline in its use. Reflux recurrence after laparoscopic antireflux surgery has not been assessed in a long-term population-based study of unselected patients.

OBJECTIVES To determine the risk of reflux recurrence after laparoscopic antireflux surgery and to identify risk factors for recurrence.

DESIGN AND SETTING Nationwide population-based retrospective cohort study in Sweden between January 1, 2005, and December 31, 2014, based on all Swedish health care and including 2655 patients who underwent laparoscopic antireflux surgery according to the Swedish Patient Registry. Their records were linked to the Swedish Causes of Death Registry and Prescribed Drug Registry.

EXPOSURES Primary laparoscopic antireflux surgery due to gastroesophageal reflux disease in adults (>18 years).

MAIN OUTCOMES AND MEASURES The outcome was recurrence of reflux, defined as use of antireflux medication (proton pump inhibitors or histamine$_2$ receptor antagonists for >6 months) or secondary antireflux surgery. Multivariable Cox regression was used to assess risk factors for reflux recurrence.

RESULTS Among all 2655 patients who underwent antireflux surgery (median age, 51.0 years; interquartile range, 40.0-61.0 years; 1354 men [51.0%]) and were followed up for a median of 5.6 years, 470 patients (17.7%) had reflux recurrence; 393 (83.6%) received long-term antireflux medication and 77 (16.4%) underwent secondary antireflux surgery. Risk factors for reflux recurrence included female sex (hazard ratio [HR], 1.57 [95% CI, 1.29-1.90]; 286 of 1301 women [22.0%] and 184 of 1354 men [13.6%] had recurrence of reflux), older age (HR, 1.41 [95% CI, 1.10-1.81] for age ≥61 years compared with ≤45 years; recurrence among 156 of 715 patients and 133 of 989 patients, respectively), and comorbidity (HR, 1.36 [95% CI, 1.13-1.65] for Charlson comorbidity index score ≥1 compared with 0; recurrence among 180 of 804 patients and 290 of 1851 patients, respectively). Hospital volume of antireflux surgery was not associated with risk of reflux recurrence (HR, 1.09 [95% CI, 0.77-1.53] for hospital volume ≤24 surgeries compared with ≥76 surgeries; recurrence among 38 of 266 patients [14.3%] and 271 of 1526 patients [17.8%], respectively).

CONCLUSIONS AND RELEVANCE Among patients who underwent primary laparoscopic antireflux surgery, 17.7% experienced recurrent gastroesophageal reflux requiring long-term medication use or secondary antireflux surgery. Risk factors for recurrence were older age, female sex, and comorbidity. Laparoscopic antireflux surgery was associated with a relatively high rate of recurrent gastroesophageal reflux disease requiring treatment, diminishing some of the benefits of the operation.

Editorial page 913

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 961

Author Affiliations: Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (Maret-Ouda, Wahlin, Lagergren); Section of Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas (El-Serag); Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (El-Serag); School of Cancer Sciences, King's College London, London, United Kingdom (Lagergren).

Corresponding Author: John Maret-Ouda, MD, Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, 171 76 Stockholm, Sweden (john.maret.ouda@ki.se).

JAMA. 2017;318(10):939-946. doi:10.1001/jama.2017.10981

Gastroesophageal reflux disease (GERD) is a public health concern in the Western world, affecting approximately 10% to 20% of all adults, and its prevalence has increased in the past 2 decades.[1,2] Complications of GERD include erosive esophagitis, esophageal strictures, Barrett esophagus, and esophageal adenocarcinoma.[3] The main treatment option for GERD is medication with proton pump inhibitors or histamine$_2$ receptor antagonists. Laparoscopic antireflux surgery with fundoplication is a treatment alternative in patients with inadequate response to pharmacological treatment.[4,5] In contrast to medication, which reduces the acidity of the refluxate, antireflux surgery creates a mechanical barrier, preventing the refluxate from passing into the esophagus. Randomized clinical trials conducted in referral centers have shown a relatively low rate of reflux recurrence (up to 15%) after antireflux surgery.[6-8] Cohort studies have shown a high risk of recurrent symptoms of GERD after surgery, which may have contributed to the decline in the use of antireflux surgery.[9-11] Recurrence of GERD after surgery can be treated with either medical therapy (proton pump inhibitor or histamine$_2$ receptor antagonist) or secondary fundoplication.[12]

The aims of our study were to assess the rate of reflux recurrence after primary laparoscopic antireflux surgery in an unselected cohort and to identify potential risk factors for such recurrence.

Key Points

Question What is the recurrence rate of gastroesophageal reflux after primary laparoscopic antireflux surgery?

Findings In this retrospective cohort study of 2655 patients who underwent primary laparoscopic antireflux surgery for gastroesophageal reflux disease in 2005-2014, reflux recurrence occurred in 17.7% (83.6% requiring long-term treatment with proton pump inhibitors or histamine$_2$ receptor antagonists, 16.4% undergoing secondary antireflux surgery).

Meaning Laparoscopic antireflux surgery was associated with a relatively high rate of recurrent gastroesophageal reflux disease requiring long-term medication or secondary antireflux surgery, diminishing some of the benefits of the operation.

Methods

Study Design

This was a nationwide population-based retrospective cohort study assessing recurrence of reflux in all individuals with a diagnosis of GERD who underwent primary laparoscopic antireflux surgery in Sweden between January 1, 2005, and December 31, 2014. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden. All data are anonymized before delivery, and individual participant informed consent is not required for this type of study according to Swedish law.

Data Collection

Data from 3 nationwide complete Swedish registries were retrieved (ie, the Patient Registry, Causes of Death Registry, and Prescribed Drug Registry), and the unique personal identity number assigned to all Swedish residents at birth or immigration was used to link individuals' data between these registries. The Patient Registry was initiated in 1964 and contains data in regard to all in-hospital and specialized outpatient health care in Sweden from 2001 onward.[13] The registry includes data about diagnoses and surgical procedures and was used to identify all individuals with GERD who underwent laparoscopic antireflux surgery during the study period in Sweden, and to collect data on comorbidities. Cohort patients were individually linked to the Prescribed Drug Registry and Causes of Death Registry to assess medication use and mortality, respectively. The Prescribed Drug Registry was initiated in 2005 and contains data on all prescribed and dispensed medications in Sweden. All prescriptions and dispensed medications in Sweden are filed electronically and automatically transferred to the Prescribed Drug Registry, and reporting is mandatory according to Swedish law. Thus, the recording is nearly 100% complete.[14] This registry includes data about all prescribed drugs with Anatomical Therapeutic Chemical classification system codes, defined daily doses, and dates of prescription and dispensation. These data were used to identify use of proton pump inhibitor and histamine$_2$ receptor antagonist. The Causes of Death Registry contains constantly updated information on the date of all deaths in Sweden since 1952. The completeness has been determined to be 100% for date of death and 99.7% for cause-specific death, and the agreement between the death certificate and manually assessed cause of death has been found to be 96.0%.[15,16] The registry was used to censor patients from follow-up from the date of death and determine the cause of death.

Exposure

All patients who underwent primary laparoscopic antireflux surgery for GERD were included in the study cohort (eAppendix 1 in the Supplement). The codes used to define GERD were 78430, 56040, 53911, and 53912 in the *International Classification of Diseases*, Seventh Revision *(ICD-7)*; 78430, 55130, 53093, and 53094 in *ICD-8*; 787B, 553D, 530B, and 530C in *ICD-9*; and R12, K44, K20, K21, and K227 in *ICD-10*. The codes representing primary laparoscopic antireflux surgery were JBC01 and JBW97 in the Nordic Medico-Statistical Committee *Classification of Surgical Procedures*. This classification system does not differentiate between types of antireflux surgery (eg, total or partial fundoplication). All participants had to be older than 18 years at the first date of GERD or at primary laparoscopic antireflux surgery, and the surgery had to be conducted after January 1, 2005. The Patient Registry was searched since its initiation in 1964 for antireflux surgery conducted before the study period (ie, January 1, 2005), enabling exclusion of all patients who had undergone antireflux surgery before the study period.

Covariates

Sex and age of the patients were retrieved from the registries used for the present study; age was defined by using the date

of birth, which was derived from the personal identity number available in the registries. Comorbidity was assessed according to data from the Patient Registry, using the most updated version of the Charlson comorbidity index, a well-validated measurement of scoring of chronic comorbidities based on specific *ICD* diagnosis codes.[17,18] All diagnoses and surgical procedures recorded in the Patient Registry since its initiation (1964) were retrieved for all study participants, and the Charlson comorbidity index score was calculated at the date of surgery. The calendar year of surgery was determined by the date of surgery in the Patient Registry. Hospital volume of antireflux surgery was determined by the unique hospital codes recorded together with the surgery in the Patient Registry. The registry does not contain data on individual surgeon volume.

Outcome

The main outcome was recurrence of reflux, which was defined according to dispensed medication of proton pump inhibitor or histamine$_2$ receptor antagonist or secondary antireflux surgery. Dispensed proton pump inhibitor or histamine$_2$ receptor antagonist corresponding to at least 6 months of medication after primary laparoscopic antireflux surgery or secondary antireflux surgery was defined as a marker of reflux recurrence. The 6-month cutoff was used to identify all individuals with recurrence of reflux requiring long-term medical treatment while excluding patients receiving such medication for other indications. Six months of treatment was defined as 6 months of defined daily doses. The World Health Organization describes defined daily doses as "the assumed average maintenance dose per day for a drug used for its main indication in adults,"[19] and they are defined for all Anatomical Therapeutic Chemical codes (eAppendix 2 in the Supplement). Use of proton pump inhibitor and histamine$_2$ receptor antagonist was identified with the Anatomical Therapeutic Chemical codes A02BC and A02BA, respectively.

Secondary antireflux surgery included both open and laparoscopic fundoplication (Nordic Medico-Statistical Committee codes JBC00, JBC01, JBW96, and JBW97) (eAppendix 2 in the Supplement). Follow-up time started at the date of surgery and ended at onset of recurrence of reflux as defined by the last dispensing of medication reaching a cumulative treatment time of 6 months, secondary antireflux surgery, death, or December 31, 2014, whichever occurred first. Furthermore, patients receiving any prescribed proton pump inhibitor or histamine$_2$ receptor antagonist, regardless of duration, were identified for descriptive purposes.

Complications

Defined procedure-related acute complications occurring within 30 days of primary laparoscopic fundoplication or repeated surgery with laparoscopic or open fundoplication were assessed from the Patient Registry. These complications included pneumothorax (*ICD-10* code J93), esophageal perforation (*ICD-10* code K223), splenic injury (*ICD-10* code S360), liver injury (*ICD-10* code S361), and other specifically surgery-associated complications (*ICD-10* code T81). To determine the risk of postoperative mortality, data in regard to date of death, as well as main and contributing causes of death, were retrieved from the Causes of Death Registry for all patients who died within 30 days of primary laparoscopic fundoplication or repeated surgery with fundoplication. In addition, all patients who had endoscopic dilatation of the esophagus (Nordic Medico-Statistical Committee code JCA55) because of stricture or dysphagia (*ICD-10* code R13) at any time after the primary or secondary laparoscopic antireflux surgery were identified.

Statistical Analysis

The statistical analyses were predefined and described in a detailed study protocol completed before the initiation of the analyses. Kaplan-Meier analysis was used to evaluate the recurrence of reflux over time after primary antireflux surgery. Patients requiring medical antireflux treatment or secondary antireflux surgery were categorized into 4 predefined intervals after the primary surgery: less than or equal to 1 year, greater than 1 to 2 years, greater than 2 to 5 years, and greater than 5 years. Separate analyses of medication and secondary surgery were also conducted in accordance with the original study protocol. A separate analysis for young and healthy individuals was added after the initially planned analyses were conducted. The risk of reflux recurrence associated with the covariates sex (male or female), age at surgery (categorized as ≤45, 46-60, or ≥61 years), comorbidity (Charlson comorbidity index score 0 or ≥1), calendar year of surgery (2005-2006, 2007-2009, or 2010-2014), and cumulative hospital volume (≤24, 25-75, or ≥76 operations per hospital during the entire study period) was analyzed with multivariable Cox regression, providing adjusted hazard ratios with 95% CIs. Thus, the level of statistical significance was .05. The assumption of proportionality was evaluated and determined to be well met. A subgroup analysis compared patients aged 45 years or younger and without comorbidity (Charlson comorbidity index score of 0), stratified by sex, with the rest of the cohort. All statistical analyses were 2-sided. The analyses were conducted with IBM SPSS Statistics version 23.

Results

The study cohort included 2655 patients with GERD who had undergone primary laparoscopic antireflux surgery between 2005 and 2014. The sex distribution was even (51.0% men). The median age at surgery was 51.0 years (interquartile range, 40.0-61.0 years). The patients were followed up for a mean of 5.1 years (SD, 2.8 years) and a median of 5.6 years (range, 0.0-9.0 years; interquartile range, 2.6-7.7 years).

Rate of Reflux Recurrence

Among all patients, 470 (17.7%) had recurrence of reflux. Among these patients, a majority received medication with proton pump inhibitor or histamine$_2$ receptor antagonist

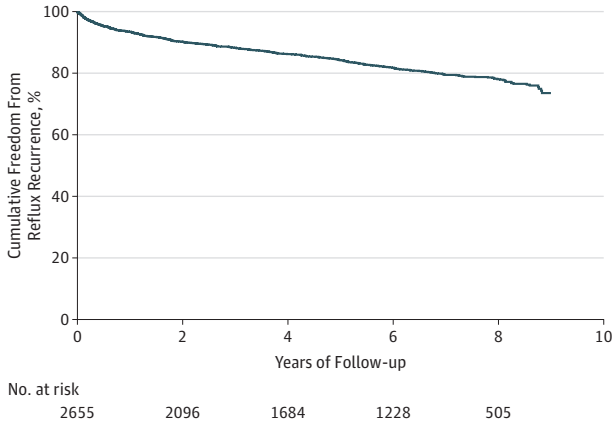
Table 1. Characteristics of Patients Who Underwent Primary Laparoscopic Antireflux Surgery in Sweden, 2005-2014

	No. (%)		
	Entire Cohort	No Recurrence of Reflux	Recurrence of Reflux
Total	2655 (100.0)	2185 (100.0)	470 (100.0)
Recurrence treated with			
Medication			393 (83.6)
Surgery			77 (16.4)
Sex			
Male	1354 (51.0)	1170 (53.5)	184 (39.1)
Female	1301 (49.0)	1015 (46.5)	286 (60.9)
Age, y			
≤45	989 (37.3)	856 (39.2)	133 (28.3)
46-60	951 (35.8)	770 (35.2)	181 (38.5)
≥61	715 (26.9)	559 (25.6)	156 (33.2)
Comorbidity score[a]			
0	1851 (69.7)	1561 (71.4)	290 (61.7)
≥1	804 (30.3)	624 (28.6)	180 (38.3)
Calendar period, y			
2005-2006	1098 (41.4)	921 (42.2)	177 (37.7)
2007-2009	802 (30.2)	656 (30.0)	146 (31.1)
2010-2014	755 (28.4)	608 (27.8)	147 (31.3)
Hospital volume[b]			
≤24	266 (10.0)	228 (10.4)	38 (8.1)
25-75	863 (32.5)	702 (32.1)	161 (34.3)
≥76	1526 (57.5)	1255 (57.4)	271 (57.7)
Reflux recurrence after surgery, y			
≤1			142 (30.2)
>1-2			87 (18.5)
>2-5			132 (28.1)
>5			109 (23.2)

[a] Charlson comorbidity index score, a measurement of chronic comorbidities based on specific diagnostic codes.

[b] Number of laparoscopic antireflux operations per hospital during the entire study period.

Figure. Kaplan-Meier Analysis Showing Patients With Recurrence of Reflux After Primary Laparoscopic Antireflux Surgery in Sweden, 2005-2014



The median follow-up duration was 5.6 years (range, 0.0-9.0 years, interquartile range, 2.6-7.7 years).

only (n = 393; 83.6%), whereas 77 patients (16.4%) underwent secondary fundoplication. Among the 77 patients, 50.6% had had herniation (n = 39). Characteristics of the participants with and without reflux recurrence are presented in **Table 1**. The reflux recurrence group contained more patients who were women, were older, and had more comorbidity compared with patients without recurrence. More patients underwent laparoscopic antireflux surgery during the initial study period; the number of surgeries decreased from 1098 in 2005-2006 to 802 in 2007-2009 to 755 in 2010-2014. A Kaplan-Meier curve was plotted to visualize the cumulative proportion of patients with reflux recurrence after primary laparoscopic antireflux surgery (**Figure**). A total of 30.2% (95% CI, 26.2%-34.5%) of the patients with reflux recurrence had recurrence during the first year after surgery, and 48.7% (95% CI, 44.2%-53.2%) had such recurrence within 2 years of surgery. During the entire study period, 1826 patients (68.8%) in the cohort received any amount of prescribed proton pump inhibitor or histamine$_2$ receptor antagonist.

Risk Factors for Reflux Recurrence

Female sex was associated with an increased risk of reflux recurrence (hazard ratio, 1.57; 95% CI, 1.29-1.90), and this risk was increased in separate analyses of need for medication and secondary fundoplication (**Table 2** and eAppendix 3 in the Supplement). Older age was associated with an increased risk of reflux recurrence, with an adjusted hazard ratio of 1.41 (95% CI, 1.10-1.81) among patients aged 61 years or older compared with those aged 45 years or younger.

Table 2. Risk Factors for Recurrence of Reflux After Primary Laparoscopic Antireflux Surgery in 2655 Patients

	Patients, Total No. (%)	Recurrence, No. (%)			Adjusted HR (95% CI) for Overall Recurrence[a]
		Overall	Treated With Medication	Treated With Surgery	
Sex					
Male	1354 (51.0)	184 (13.6)	154 (11.4)	30 (2.2)	1 [Reference]
Female	1301 (49.0)	286 (22.0)	239 (18.4)	47 (3.6)	1.57 (1.29-1.90)
Age, y					
≤45	989 (37.3)	133 (13.4)	107 (10.8)	26 (2.6)	1 [Reference]
46-60	951 (35.8)	181 (19.0)	149 (15.7)	32 (3.4)	1.28 (1.02-1.61)
≥61	715 (26.9)	156 (21.8)	137 (19.2)	19 (2.7)	1.41 (1.10-1.81)
Comorbidity score[b]					
0	1851 (69.7)	290 (15.7)	234 (12.6)	56 (3.0)	1 [Reference]
≥1	804 (30.3)	180 (22.4)	159 (19.8)	21 (2.6)	1.36 (1.13-1.65)
Year of surgery					
2005-2006	1098 (41.4)	177 (16.1)	138 (12.6)	39 (3.6)	1 [Reference]
2007-2009	802 (30.2)	146 (18.2)	123 (15.3)	23 (2.9)	1.61 (1.27-2.03)
2010-2014	755 (28.4)	147 (19.5)	132 (17.5)	15 (2.0)	3.86 (2.98-5.02)
Hospital volume[c]					
≤24	266 (10.0)	38 (14.3)	30 (11.3)	8 (3.0)	1 [Reference]
25-75	863 (32.5)	161 (18.7)	144 (16.7)	17 (2.0)	1.13 (0.79-1.62)
≥76	1526 (57.5)	271 (17.8)	219 (14.4)	52 (3.4)	1.09 (0.77-1.53)

Abbreviation: HR, hazard ratio.

[a] Adjusted for sex, age, comorbidity, calendar year, and hospital volume, other than the variable in that row.

[b] Charlson comorbidity index score, a measurement of chronic comorbidities based on specific diagnostic codes.

[c] Number of laparoscopic antireflux operations per hospital during the entire study period.

When analyzed separately, the association with age remained for medication, but not for repeated surgery (eAppendix 3 in the Supplement). Patients with comorbidity (Charlson comorbidity index score ≥1) were at increased risk of reflux recurrence compared with those without comorbidity (hazard ratio, 1.36; 95% CI, 1.13-1.65). The association between increased Charlson comorbidity index scores and an increased risk of reflux recurrence remained in separate analysis of only medication as the outcome, but not in the analysis assessing only secondary fundoplication.

Among 799 participants (559 men and 240 women) aged 45 years or younger and without comorbidity (Charlson comorbidity index score 0), 62 men (11.1%) and 41 women (17.1%) had recurrence. The risk of recurrence was decreased among both men (hazard ratio, 0.66; 95% CI, 0.49-0.90) and women (hazard ratio, 0.67; 95% CI, 0.48-0.93) compared with the remaining participants. The risk of recurrence increased during the study period, from 16.1% in 2005-2006 to 19.5% in 2010-2014 (hazard ratio, 3.86; 95% CI, 2.98-5.02; $P < .001$), but this increase was statistically significant only for medication as outcome (hazard ratio, 5.20; 95% CI, 3.86-7.01) and not for secondary fundoplication (hazard ratio, 1.20; 95% CI, 0.64-2.24) (eAppendix 3 in the Supplement). The index surgeries were performed in a total of 52 centers (volume, 1-718 surgeries). No statistically significant associations were found between hospital volume of antireflux surgery and the risk of reflux recurrence after primary laparoscopic antireflux surgery (comparing ≤24 surgeries and ≥76 surgeries; hazard ratio, 1.09; 95% CI, 0.77-1.53) (Table 2).

Complications After Antireflux Surgery

In all, 109 patients (4.1%) had a defined complication within 30 days of the primary laparoscopic antireflux surgery, and the most common complications were infection (n = 28; 1.1%), bleeding (n = 24; 0.9%), and esophageal perforation (n = 24; 0.9%) (**Table 3**). The 30-day all-cause mortality rate was 0.1% (n = 2 patients, 1 because of inhalation of a foreign body and 1 because of suicide). During the entire postoperative follow-up, 21 patients (0.8%) received a diagnosis of dysphagia at any time, including 14 (0.5%) also requiring endoscopic dilatation.

In regard to secondary fundoplication, 18 patients (23.4%) had a complication within 30 days of surgery, and the most common complications were infection (n = 5; 6.5%), esophageal perforation (n = 5; 6.5%), and bleeding (n = 4; 5.2%) (Table 3). There were no deaths within 30 days after secondary fundoplication. Nineteen patients (24.7%) received a diagnosis of dysphagia, and 8 of these (10.4%) underwent endoscopic dilatation during follow-up.

Discussion

This study found that 17.7% of patients had recurrence of reflux after primary laparoscopic antireflux surgery. Risk factors for recurrence were female sex, older age, and comorbidity, whereas hospital volume was not a risk factor. Young individuals without comorbidity had a lower risk of reflux recurrence compared with the remaining participants.

The current study's percentage of patients with recurrent reflux (17.7%) is lower than that of most cohort studies. Randomized clinical trials show recurrence rates similar to that of the present study, ranging between 10% and 15% after 3 to 5 years,[6-8] but these trials do not mirror clinical practice well because they included highly selected patients at specialized centers. Among cohort studies including 98 to 844 patients, with a follow-up time ranging from 1 to 6 years, the proportion of patients requiring antireflux treatment after

Table 3. Complications Within 30 Days After Primary Laparoscopic Antireflux Surgery and Secondary Antireflux Surgery

Complication	Patients, No. (%)	
	Primary Antireflux Surgery (n = 2655)	Secondary Antireflux Surgery (n = 77)
Overall complications	109 (4.1)	18 (23.4)
Mortality	2 (0.1)	0
Infection	28 (1.1)	5 (6.5)
Bleeding	24 (0.9)	4 (5.2)
Esophageal perforation	24 (0.9)	5 (6.5)
Pneumothorax	5 (0.2)	1 (1.3)
Splenic injury	4 (0.2)	0
Vascular injury	3 (0.1)	0
Liver injury	1 (<0.1)	0
Wound rupture	1 (<0.1)	1 (1.3)
Nonspecified	28 (1.1)	4 (5.2)

primary laparoscopic antireflux surgery ranged from 4% to 43%.[9-11,20-22] Highest rates of postoperative antireflux medication were found in 4 studies with rates between 33% and 43%.[9-11,22] In regard to secondary fundoplication, a study of 297 patients found that 17 (5.7%) required secondary fundoplication within 2 years of primary surgery,[21] a rate similar to that in a recent study of 9765 patients, in which 540 (5.5%) underwent secondary antireflux surgery.[23]

There are several possible reasons for the findings of lower recurrence rate compared with that in many other cohort studies. The present study used a population-based design and had a larger sample size and more complete follow-up than previous cohort studies. This study also assessed a more recent period, in which laparoscopic antireflux surgery has become more centralized to expert centers where selection of patients might be stricter and the quality of surgery might be higher.

In the present study, women had a slightly higher risk of recurrence of GERD after antireflux surgery than men. Similar results were observed in a cohort study of 844 patients.[9] The higher rate of postoperative medication among women might be explained by their having more severe symptoms of GERD despite having endoscopic severity of GERD similar to that of men.[24] Age was another factor that was associated with an increased risk of reflux recurrence after fundoplication. Similar results have been shown in some earlier studies,[9,25] although other investigations have found contradictory results.[26,27] The consequence of comorbidities on the rate of recurrence of GERD after laparoscopic antireflux surgery has, to the best of our knowledge, not been studied before. It is possible that the increased risk of reflux recurrence associated with older age and comorbidities exists because only patients with particularly severe and refractory GERD in these groups are selected for surgery, and these patients might also be at a higher risk of recurrence of reflux. Additionally, it is possible that these groups are more likely to have large hiatal hernias, which might reduce the success of antireflux surgery because of difficulties in repairing large hiatal defects. Previous research has found that larger hospital volumes are associated with more favorable outcomes, especially in regard to cancer surgery.[28,29] However, no association between hospital volume and the risk of recurrence of GERD after primary laparoscopic antireflux surgery was observed in the present study.

The complication rates after primary and secondary fundoplication were similar to those of previous reports, with a higher complication rate associated with secondary surgery.[30,31] The low all-cause mortality rate (with no direct surgery-related deaths) found in the current cohort is also similar to that of previous research.[30,32] The higher risks of recurrence among older and female patients and patients with comorbidities suggest that laparoscopic antireflux surgery might be more successful in younger and physically fit individuals, which is supported by the present analysis of this subgroup and well aligned with previous research.[5] Additionally, previous studies suggest that long-term treatment with proton pump inhibitors might be associated with adverse events, including an increased risk of hip fractures, *Clostridium difficile*–associated diarrhea, and community-acquired pneumonia.[33-36] Most available studies show that antireflux surgery is more expensive in the short term, but more cost-effective from a long-term perspective.[37]

A strength of this study is the population-based design with virtually complete nationwide coverage of patients with GERD who have undergone primary laparoscopic antireflux surgery. This design reflects general clinical practice, minimizes selection bias, and circumvents recall bias. Other advantages are the high completeness, accuracy, and quality of the Swedish registry data used for this study. The registries are based on data submitted from hospitals after patient discharge, which is necessary for reimbursement of health care costs and contributes to the complete information recorded. Furthermore, all patients are readily followed up through use of their personal identity numbers regardless of where they seek health care, when they die, or whether they emigrate. Thus, there are no patients lost to follow-up, which is a major strength of the study.

Limitations

This study has several limitations. First, there might be variations in clinical practice in regard to coding, especially for diagnoses that are not the primary reason the patient seeks health care. Second, data on unmeasured confounders (eg, body mass index, tobacco smoking) were not available in the registries. Although this might have influenced the risk factor analyses, the main outcome, overall rate of reflux recurrence after primary laparoscopic fundoplication, was not affected by any residual confounding. Third, the current study design did not include a control group (eg, a group of patients with GERD who did not undergo antireflux surgery). Such a group would be of value to better compare the rate of recurrence among individuals who had surgery compared with those who did not. Fourth, there is uncertainty about whether the definition of reflux recurrence used was accurate. There was no information about objectively identified reflux recurrence (ie, from endoscopies or pH measurements). However, studies have shown a poor correlation between postoperative reflux symptoms and GERD assessed

with objective measurements, which casts the sensitivity of such measurements in doubt.[38] Fifth, information about reflux symptoms was not available. However, such symptoms have a low specificity when recurrence of reflux is assessed. The use of treatment of reflux (medical or surgical) circumvents the low sensitivity and specificity of the alternative measures presented above and is thus probably the best currently available option to assess the recurrence of reflux. Sixth, use of proton pump inhibitors or histamine$_2$ receptor antagonists bought over the counter might be a concern, which was not possible to assess in this study and may have introduced underestimation of reflux recurrence. However, these medications are sold over the counter only in small packages and at a high price, whereas dispensed prescriptions are less expensive and eventually free of charge (state-subsidized) in a progressive discount system, in which the patient pays maximum 2200 Swedish crowns (approximately $250) annually for prescribed medications. Thus, patients who require medical treatment for a longer period would likely have obtained prescriptions. The 6-month use cutoff was arbitrary, but a shorter period might have increased the misclassification of use of proton pump inhibitor or histamine$_2$ receptor antagonist for other indications (eg, ulcer, occasional dyspepsia), supported by the fact that a majority of patients (n = 1826; 68.8%) received occasional prescriptions of proton pump inhibitor or histamine$_2$ receptor antagonist during the study period. The assessment of secondary antireflux surgery should be complete, but some of these surgeries were conducted for dysphagia, although this rate was low (n = 6).

Conclusions

Among patients who underwent laparoscopic antireflux surgery, 17.7% experienced recurrent GERD requiring long-term medication use or secondary antireflux surgery. Laparoscopic antireflux surgery was associated with a relatively high rate of recurrent GERD requiring long-term treatment, diminishing some of the benefits of the operation.

ARTICLE INFORMATION

Accepted for Publication: July 25, 2017.

Author Contributions: Dr Lagergren had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Maret-Ouda, El-Serag, Lagergren.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Maret-Ouda.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Maret-Ouda, Wahlin.
Obtained funding: Lagergren.
Supervision: Lagergren.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was funded by the Swedish Research Council (grant D0547801).

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

REFERENCES

1. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. *Gut*. 2012;61(10):1390-1397.

2. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*. 2014;63(6):871-880.

3. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. *Lancet*. 2017;S0140-6736(17)31462-9.

4. Harnik IG. In the clinic: gastroesophageal reflux disease. *Ann Intern Med*. 2015;163(1):ITC1.

5. Maret-Ouda J, Brusselaers N, Lagergren J. What is the most effective treatment for severe gastro-oesophageal reflux disease? *BMJ*. 2015;350:h3169.

6. Lundell L, Attwood S, Ell C, et al; LOTUS Trial Collaborators. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. *Gut*. 2008;57(9):1207-1213.

7. Grant AM, Boachie C, Cotton SC, et al; REFLUX Trial Group. Clinical and economic evaluation of laparoscopic surgery compared with medical management for gastro-oesophageal reflux disease: 5-year follow-up of multicentre randomised trial (the REFLUX trial). *Health Technol Assess*. 2013;17(22):1-167.

8. Anvari M, Allen C, Marshall J, et al. A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for the treatment of patients with chronic gastroesophageal reflux disease (GERD): 3-year outcomes. *Surg Endosc*. 2011;25(8):2547-2554.

9. Wijnhoven BP, Lally CJ, Kelly JJ, Myers JC, Watson DI. Use of antireflux medication after antireflux surgery. *J Gastrointest Surg*. 2008;12(3):510-517.

10. Gee DW, Andreoli MT, Rattner DW. Measuring the effectiveness of laparoscopic antireflux surgery: long-term results. *Arch Surg*. 2008;143(5):482-487.

11. Bonatti H, Bammer T, Achem SR, et al. Use of acid suppressive medications after laparoscopic antireflux surgery: prevalence and clinical indications. *Dig Dis Sci*. 2007;52(1):267-272.

12. Patti MG, Allaix ME, Fisichella PM. Analysis of the causes of failed antireflux surgery and the principles of treatment: a review. *JAMA Surg*. 2015;150(6):585-590.

13. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish National Inpatient Register. *BMC Public Health*. 2011;11:450.

14. National Board of Health and Welfare. Swedish prescribed drug register. http://www.socialstyrelsen.se/register/halsodataregister/lakemedelsregistret/bortfallochkvalitet. Accessed February 1, 2017.

15. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol*. 2000;29(3):495-502.

16. Godtman R, Holmberg E, Stranne J, Hugosson J. High accuracy of Swedish death certificates in men participating in screening for prostate cancer: a comparative study of official death certificates with a cause of death committee using a standardized algorithm. *Scand J Urol Nephrol*. 2011;45(4):226-232.

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

18. Armitage JN, van der Meulen JH; Royal College of Surgeons Co-morbidity Consensus Group. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg*. 2010;97(5):772-781.

19. World Health Organization. Defined daily dose: definition and general considerations. https://www.whocc.no/ddd/definition_and_general_considera/. Accessed December 14, 2016.

20. Ciovica R, Riedl O, Neumayer C, Lechner W, Schwab GP, Gadenstätter M. The use of medication after laparoscopic antireflux surgery. *Surg Endosc*. 2009;23(9):1938-1946.

21. Papasavas PK, Keenan RJ, Yeaney WW, Caushaj PF, Gagné DJ, Landreneau RJ. Effectiveness of laparoscopic fundoplication in relieving the symptoms of gastroesophageal reflux disease

(GERD) and eliminating antireflux medical therapy. *Surg Endosc*. 2003;17(8):1200-1205.

22. 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(12):1824-1830.

23. Maret-Ouda J, Lagergren J. The risk of mortality following secondary fundoplication in a population-based cohort study. *Am J Surg*. 2017;213(6):1160-1162.

24. Lin M, Gerson LB, Lascar R, Davila M, Triadafilopoulos G. Features of gastroesophageal reflux disease in women. *Am J Gastroenterol*. 2004;99(8):1442-1447.

25. Jackson PG, Gleiber MA, Askari R, Evans SR. Predictors of outcome in 100 consecutive laparoscopic antireflux procedures. *Am J Surg*. 2001;181(3):231-235.

26. Fei L, Rossetti G, Moccia F, et al. Is the advanced age a contraindication to GERD laparoscopic surgery? results of a long term follow-up. *BMC Surg*. 2013;13(suppl 2):S13.

27. Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? preoperative prediction of long-term outcomes. *Surg Endosc*. 2007;21(11):1978-1984.

28. Brusselaers N, Mattsson F, Lagergren J. Hospital and surgeon volume in relation to long-term survival after oesophagectomy: systematic review and meta-analysis. *Gut*. 2014;63(9):1393-1400.

29. Liu CJ, Chou YJ, Teng CJ, et al. Association of surgeon volume and hospital volume with the outcome of patients receiving definitive surgery for colorectal cancer: a nationwide population-based study. *Cancer*. 2015;121(16):2782-2790.

30. Niebisch S, Fleming FJ, Galey KM, et al. Perioperative risk of laparoscopic fundoplication: safer than previously reported—analysis of the American College of Surgeons National Surgical Quality Improvement Program 2005 to 2009. *J Am Coll Surg*. 2012;215(1):61-68.

31. van Beek DB, Auyang ED, Soper NJ. A comprehensive review of laparoscopic redo fundoplication. *Surg Endosc*. 2011;25(3):706-712.

32. Richter JE. Gastroesophageal reflux disease treatment: side effects and complications of fundoplication. *Clin Gastroenterol Hepatol*. 2013;11(5):465-471.

33. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA*. 2006;296(24):2947-2953.

34. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2011;106(7):1209-1218.

35. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. *Clostridium difficile*–associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol*. 2012;107(7):1001-1010.

36. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? a meta-analysis. *Expert Rev Clin Pharmacol*. 2012;5(3):337-344.

37. Gawron AJ, French DD, Pandolfino JE, Howden CW. Economic evaluations of gastroesophageal reflux disease medical management. *Pharmacoeconomics*. 2014;32(8):745-758.

38. Khajanchee YS, O'Rourke RW, Lockhart B, Patterson EJ, Hansen PD, Swanstrom LL. Postoperative symptoms and failure after antireflux surgery. *Arch Surg*. 2002;137(9):1008-1013.