2016-09-29

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Br J Surg. 2016 Jun;103(7):863-70.
http://doi.org/10.1002/bjs.10141
http://hdl.handle.net/10616/45302

Mortality from primary laparoscopic antireflux surgery in a population-based cohort study

Running title: Mortality from primary laparoscopic antireflux surgery

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Keywords: Gastro-oesophageal reflux disease, Fundoplication, Laparoscopic surgery, Reoperation, Hospital stay

Funding Source: The Swedish Research Council (grant number D0547801).

Category of article: Original article

Word count: 2970

The paper, or any data presented in it, is not based on previous communication to a society or a meeting.

ABSTRACT

Background: Effective treatment of severe gastro-oesophageal reflux disease is available through medication or surgery. Postoperative risks have contributed to decreased use of antireflux surgery. We aimed to assess short-term mortality following primary laparoscopic fundoplication.

Method: Population-based nationwide Swedish cohort study including all Swedish hospitals performing laparoscopic fundoplication, between 1997 and 2013. All patients aged 18-65 years with gastro-oesophageal reflux disease who underwent primary laparoscopic fundoplication during the study period were included. Main outcome was absolute all-cause and surgery-related 90-day and 30-day mortality. Secondary outcomes were reoperation and length of hospital stay. Logistic regression was used to calculate odds ratios with 95% confidence intervals of reoperation within 90 days and prolonged hospital stay (≥4 days).

Results: Of 8947 included patients, 5306 (59.3%) were men, and 551 (6.2%) had a significant comorbidity (Charlson comorbidity score >0). Median age at surgery was 48 years, and median hospital stay was 2 days. Annual rate of laparoscopic fundoplication decreased from 15.3 to 2.4 cases per 100 000 inhabitants during the study period, while the proportion of patients with comorbidity increased more than 2-fold. All-cause 90- and 30-day mortality were 0.08% (n=7) and 0.03% (n=3), respectively. Only 1 death (0.01%) was directly surgery-related. 90-day reoperation rate was 0.4% (n=39). Comorbidity and higher age entailed increased risk for prolonged hospital stay, but not for reoperation.

Conclusion: This population-based study revealed a remarkably low 90-day mortality and reoperation rate following laparoscopic, results which might influence clinical decision-making in the treatment of severe gastro-oesophageal reflux disease.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a public health concern, affecting 10% to 20% of all adults in Western populations, and the rate is increasing.[1] GORD is associated with limitations to quality of life, high costs for patients, healthcare and society, and a risk of complications, including oesophageal adenocarcinoma; an increasingly common cancer with poor prognosis.[1-4] The two most effective treatment options for severe GORD are continuous and long-term medication with proton pump inhibitors (PPIs) or anti-reflux surgery with laparoscopic fundoplication.[2, 3] In current practice, surgery is typically only recommended to GORD patients who experience an inadequate response to PPIs or who object to long-term use of PPIs. The literature indicates that laparoscopic fundoplication may be superior to PPI treatment in terms of reflux symptoms, oesophageal acid exposure, overall and GORD associated quality of life, prevention of oesophageal adenocarcinoma, and long-term cost effectiveness.[3, 5] However, the risk of mortality and morbidity following anti-reflux surgery has strongly contributed to its considerably decreased use in the last decade,[2, 6, 7] although studies suggest that surgical therapy might be under-utilized.[2, 6-8] The reported overall perioperative and 30-day mortality is 0.45%,[2, 6, 7, 9] and severe complications occur in up to 4%,[2, 3, 10] which is not negligible for a benign disorder. However, studies addressing mortality and morbidity following anti-reflux surgery are mostly at least a decade old, or have been of the scale of examining only single or multiple institutions. Only two population-based studies are available, one assessed inpatient postoperative mortality and morbidity,[6] and one assessed 30-day mortality.[9] Yet, in an era demonstrating great improvements in postoperative care, 90-day mortality might be a better assessment of postoperative mortality in upper gastrointestinal surgery.[11] We aimed to assess 90-day mortality and morbidity after primary laparoscopic fundoplication for GORD in a recent and unselected nationwide cohort with complete follow-up of all participants.

METHODS

Study design

This was a nationwide, Swedish population-based cohort study investigating the absolute risk of mortality and reoperation up to 90 days following primary laparoscopic fundoplication during the study period 1st January 1997 to 31st December 2013. In addition, the relative risks of reoperation and prolonged postoperative hospital stay were assessed. The study cohort consisted of all patients aged 18 to 65 years who underwent laparoscopic fundoplication for a recorded GORD diagnosis in Sweden during the study period. Data were collected from nationwide Swedish registries. The unique 10-digit personal identity number assigned to each resident in Sweden upon birth or immigration, enabled linkages of individuals' data between registries. The indication for surgery, the surgical technique used, as well as cause of death, was validated through retrieval of medical records for patients who died within 90 days postoperatively during the study period. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (reference number 2014/234-31).

Exposure

All eligible patients, i.e. those who underwent laparoscopic fundoplication for GORD during the study period, were identified from the *Swedish Patient Registry*. We used GORD as a criteria for inclusion to avoid including fundoplication for other indications. Excluded were 290 patients without a GORD-related diagnosis recorded, including 8 of with a Charlson score >1. None of these patients died within 90 days of surgery. The vast majority of these patients had a fundoplication in association with oesophago-gastric myotomies, mainly for achalasia. The Patient Registry records in-hospital and outpatient care since 1964, and includes discharge diagnoses, comorbidities, surgical procedures, hospitalization dates, and demographic data. The coverage of in-hospital care has been

nationwide complete since 1987**,** and the coverage of outpatient specialist care reached 100% in 2001.[12] The documented data regarding both diagnoses and surgical procedures have excellent completeness and validity.[12, 13] The NOMESCO Classification of Surgical Procedures, which provides separate codes for laparoscopic and open anti-reflux procedures, was introduced to the Patient Registry in 1997, thus determining the start date of the study. Laparoscopic fundoplication was identified using the NOMESCO code 'JBC-01', and reoperations were identified with any NOMESCO code beginning with 'JW'. The Patient Registry does not contain data on the subtype of fundoplication performed, e.g. procedures according to Nissen, Toupet or others. The data needed to calculate the rates of laparoscopic fundoplication per 100 000 inhabitants between 18 and 65 years in Sweden were derived from the Patient Registry and the *Swedish Registry of the Total Population*. The latter Registry has had 100% nationwide completeness since 1947.[14] GORD diagnoses were retrieved from the Patient Registry (using the International Classification of Diseases versions 7-10): GORD, heartburn, hiatal hernia, oesophagitis and Barrett's oesophagus. Also very large hiatal hernias were included.

Outcomes

Date and causes of death were identified from the *Swedish Causes of Death Registry*. This Registry contains information on all deceased Swedish residents since 1952 with a completeness of 99.2%.[15] All data in this Registry are coded according to the International Classification of Diagnoses system.

Data on the secondary outcomes, i.e. postoperative reoperation and prolonged hospital stay, were retrieved from the Patient Registry. Postoperative reoperation was defined as any surgery conducted within 90 days following the primary fundoplication. Patients who died within 90 days of surgery were excluded from the analyses addressing reoperation.

Prolonged hospital stay was defined as duration of stay of 4 or more days following laparoscopic fundoplication, which exceeds the routine length of stay.[2, 16] Length of hospital stay was calculated from the admission and discharge dates in the Patient Registry. In order to include any in-hospital days following discharge at another ward or hospital, we also included any subsequent in-hospital care following admissions up to 1 day after discharge from the surgery ward.

Covariates

The study covariates were sex, age, comorbidity, date of admission, and length of hospital stay, all collected from the Patient Registry. Covariates were chosen based on known cause-effect relations for increased morbidity and mortality in the previous literature. The covariates and the model was determined in the study protocol prior to data collection to ensure nominal coverage of the confidence intervals. Comorbidity was defined using the Charlson comorbidity score, a well validated composite variable for quantification of comorbidity, which is based on specific diagnosis codes.[17-20] Patients were categorized into three Charlson comorbidity score groups: 0, 1, or $\geq$2, a categorization that distinguishes the groups regarding risk of mortality.[17]

Statistical analysis

We calculated the absolute risk of death and reoperation following laparoscopic fundoplication. The low number of deaths prohibited further analyses of short-term mortality. A multivariable logistic regression model was used to assess the odds ratio (OR) and 95% confidence interval (CI) of reoperation within 90 days after surgery, as well as of prolonged length of hospital stay. Adjustments were made for the covariates age (continuous variable), sex (male or female), year of surgery (continuous variable), and Charlson comorbidity score (0, 1, or $\geq$2). Model assumptions and goodness of fit

were checked formally and graphically.[21] The residuals were plotted against fitted values to assess (lack of) fit graphically. We checked for overly influential observations using a plot of Cook's distance versus leverage. Overdispersion was checked by fitting a quasibinomial instead of a binomial. In the analysis of hospital stay, a thin plate regression spline was used to model the effect of year of surgery. The number of knots was checked using a simulation approach. While the exact basis dimension of a thin-plate spline is not generally critical, a small enough number ensures computational efficiency.[22] We used the simulation approach described and implemented in the mgcv package for R, as described previously.[23] Briefly, an estimate of the residual variance of near neighbours was calculated. Residuals were reshuffled a number of times to obtain the null distribution of the differencing variance estimator (i.e., there was no pattern present in the residuals given the chosen basis dimension). The analyses were conducted using the statistical software SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA) and R.[24]

Role of the funding source

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Study participants

In total, 8947 patients constituted the laparoscopic fundoplication study cohort with a median age at surgery of 48 years, and median length of hospital stay of 2 days (Table 1). The majority were men (n=5306, 59.3%), and 5.5% (n=488) and 0.7 % (n=63) had a Charlson score of 1 or ≥2, respectively. The annual number of laparoscopic fundoplication procedures decreased from 832 in 1997 to 144 in 2013 (Figure 1A), and the annual procedures performed per 100 000 inhabitants decreased from 15.3 cases in 1997 to 2.4 cases in 2013 (Figure 1B). The proportion of women increased from 40.7% in 1997 to 48.6% in 2013. During the study period, the proportion of patients with a Charlson comorbidity score of 1 and ≥2 increased more than 2-fold and 3-fold, respectively (Figure 2). The distribution in age and length of hospital stay remained constant throughout the study period.

Mortality

Seven patients died within 90 days of surgery, of whom 3 died within 30 days, giving 90-day and 30-day all-cause mortality rates of 0.08% and 0.03%, respectively (Table 1). One patient (0.01%) died from a direct surgery-related complication, an acute respiratory distress syndrome, 19 days after surgery, which was the only in-hospital death. The causes of the other 6 deaths were heart failure (n=2), suicide (n=2), diabetic ketoacidosis (n=1), and accidental poisoning (n=1). The indications for surgery and surgical technique used among all patients that died within 90 days were validated through medical records, and were found to be accurate in all cases. The number of all-cause deaths did not surpass 1 in any of the 17 years studied (Figure 1A). None of the deceased patients underwent reoperation. Compared to the other participants, patients who died within 90 days of fundoplication had a longer median hospital stay (11 versus 2 days) and more

comorbidities with a Charlson score of 1 (28.6% versus 5.5%) and ≥2 (14.3% versus 0.7%), whereas the distribution of sex and age was similar.

Reoperation

The reoperation rate was 0.4% (n=39) within 90 days of laparoscopic fundoplication, and also 0.4% (n=38) within 30 days of surgery. In 1997, 3 reoperations were conducted, reaching an annual maximum of 6 in 2000, and with no frequency above 1 per year from 2008 onwards (Figure 1A). The distribution of age, sex, and comorbidity was similar in the 90-day reoperation group and the other study participants, while median length of hospital stay was greater in the reoperation group (6 versus 2 days) (Table 1). There were no statistically significant associations between age, sex, year of surgery, or comorbidity, and risk of reoperation (Table 2).

Prolonged hospital stay

Comorbidity, female sex, and higher age were associated with an increased risk of prolonged hospital stay (Table 2). The risk of prolonged hospital stay was characterized by a complex pattern over time, descending from increased risk to decreased risk in the early to intermediate years of the study, followed by a slight surge during the most recent 6 years (Figure 3). Overall the risk declined over the study period, especially from the start of the study period to 2005, after 2005 there was a slight increase (Figure 3).

DISCUSSION

This study found a very low 90-day all-cause (0.08%) and procedure-related mortality rate (0.01%), and reoperation rate (0.4%) following laparoscopic fundoplication for GORD. The increasing proportion of operated patients with comorbidity over time did not translate into any increase in mortality, reoperation or hospital stay.

Methodological strengths of this study include the nationwide coverage and population-based design, including virtually all GORD patients who underwent laparoscopic fundoplication in Sweden in 1997-2013, which abates selection bias, facilitates generalizability, and provides a large sample size. Moreover, the complete and well-maintained nationwide registries available in Sweden enabled complete follow-up of all participants, thus avoiding loss to follow-up. Among potential weaknesses of the study is a risk of clinical selection of relatively healthy patients for surgery, yet often with particularly severe GORD. However, the surgery cohort reflects routine clinical practice and should have only a limited effect on generalizability of the results. Moreover, the increasing presence of comorbidity over time did not increase the risk of unfavourable short-term outcomes. Since laparoscopic fundoplication can be performed also for indications other than GORD, a GORD diagnosis was required for inclusion. Although this makes the study more valid, it also introduces a risk of missing eligible individuals who had GORD, but did not have this diagnosis recorded. However, this error should be limited since discharge diagnoses are required to be recorded in the hospital discharge notes, which are transferred to the Swedish Patient Registry. Although adjustments for several potential confounding factors were made, information on some other potential confounders was not available, including tobacco smoking, which can increase the risk of postoperative complications. However, long-term smoking was indirectly adjusted for through adjustment for the Charlson comorbidity score, which included chronic

obstructive pulmonary disorder, a proxy diagnosis for tobacco smoking. Moreover, it is unlikely that information on tobacco smoking would change any of the main results. Finally, owing to the partial lack of data regarding exact date of surgery, the date of admission was used as a proxy. This assumption could have resulted in slightly imprecise postoperative follow-up dates.

To our knowledge, this is the first study investigating 90-day mortality and morbidity rates following laparoscopic fundoplication in unselected GORD patients. A Cochrane systematic review including 4 randomized clinical trials, all conducted during 1997-2004 (total n=519), comparing laparoscopic fundoplication and PPI treatment in GORD patients reported 0 inpatient deaths (all trials), 3.7% 90-day reoperation rate (one trial), and 0 reoperations within 1 year (two trials).[7] Furthermore, a recent large cohort study from the United States (n=78 233) conducted in 2005-2010 revealed an inpatient mortality of 0.13% (calculated by us),[6] and a population-based cohort study from Denmark (n=2465) between 1997 and 2005 found a 30-day mortality of 0.45%,[9] both substantially higher than in our study (0.01%). It was not possible to calculate the mortality within 30 or 90 days of surgery in the cohort study from the United States, but the inpatient complication rate for each year studied showed a higher peak (8.1% versus 0.7%) and trough (6.3% versus 0.0%) compared to our study.[6] The higher inpatient mortality in the previous study might partly be explained by the inclusion of patients of older age and with greater comorbidity. Another cohort study from the United States (n=7531) performed in 2005-2009, which evaluated mortality in patients aged less than 70 years, showed a 30-day mortality rate of 0.05%, which is more similar to the present study (0.03%). However, that study reported a higher complication rate (1.8%).[2] Finally, an older Finnish nationwide cohort study (n=6859) conducted in 1992-2001 revealed a

30-day mortality rate of 0.04%,[10] which is similar to the present study. However, the Finnish study did not assess surgery-related or 90-day mortality.

The present study found a higher prevalence of comorbidity in the 7 patients who died within 90 days of laparoscopic fundoplication, which indicates that comorbidity should be taken into account when the treatment alternatives are considered. However, the increasing proportion of patients with comorbidity during the study period did not seem to have affected the risk of poor 90-day outcomes.[6] Possible explanations are advancement in the modern laparoscopic fundoplication technique, enhanced surgeon skills, centralization of services or improvements in perioperative healthcare.

The increased risk of prolonged hospital stay with higher age and comorbidity in this study could be explained by their greater disposition to postoperative complications and slower recovery compared to younger and fitter patients. Speculatively, a higher proportion of women with obesity and increased length of surgery could explain the higher risk of prolonged hospital stay found in female patients, since these factors correlate with prolonged hospital stay in other upper gastrointestinal surgery patients.[25]

A decreased use of fundoplication with calendar time has also been reported in the United States, where the use of anti-reflux surgery declined from 15.7 to 5.3 operations per 100,000 inhabitants between 1999 and 2010.[6, 26] This decline could be attributed to the increased use of PPIs since the early 2000s, an easily accessible drug proven to be effective in reflux control and with a well-documented and safe profile.[3, 27] In addition, the potential risks of mortality and morbidity associated with anti-reflux surgery appear to have led general practitioners, gastroenterologists, and possibly also surgeons to predominantly favour PPIs over surgery for GORD treatment. Yet, both treatment options

can effectively counteract GORD and improve quality of life, although surgery appears to be slightly superior in these respects.[3] Recurrence of GORD is similarly common following both treatments,[3] while surgery might be more effective in preventing oesophageal adenocarcinoma than PPI use.[5] Moreover, surgery seems to be more costly in the short term, but perhaps more cost-effective in the long term.[3] In addition, concerns regarding increased risk of osteoporosis, bone fractures, and *Clostridium difficile*-associated diarrhoea following long-term treatment with PPIs have arisen.[3]

This study demonstrates that laparoscopic fundoplication offers a remarkably safe alternative to long-term PPI therapy for severe GORD, with a risk profile similar to other common laparoscopic procedures for benign diagnoses, i.e. appendectomy and cholecystectomy.[2] The low risk might at least partly be due to the increased specialization of surgeons involved in minimally invasive upper gastrointestinal surgery. The slight superiority of laparoscopic fundoplication treatment, along with the treatment's safe profile, and the increasingly recognized complications of long-term PPI use, argue for adopting a decrease in the threshold for recommending laparoscopic fundoplication in severe GORD patients, particularly in fit patients aged below 65 years.

In conclusion, this large and population-based cohort study with complete follow-up shows a remarkably low surgery-related and all-cause mortality and reoperation rate within 90 days following primary laparoscopic fundoplication for GORD. These results suggest that laparoscopic fundoplication can be recommended as a safe alternative to PPI treatment in fit patients aged below 65 years, at least in the short-term perspective.

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Table 1. Characteristics of 8947 patients who underwent laparoscopic fundoplication for gastro-oesophageal reflux disease during 1997-2013 in Sweden.

	All patients Number (%)	90-day death Number (%)	90-day reoperation Number (%)
Total	8947 (100.0)	7 (0.08)	39 (0.4)
Age at surgery, median years (Interquartile range)	48 (38-55)	42 (41-61)	51 (39-56)
Sex			
Male	5306 (59.3)	4 (57.1)	21 (53.9)
Female	3641 (40.7)	3 (42.9)	18 (46.1)
Comorbidity (Charlson score)*			
0	8396 (93.8)	4 (57.1)	35 (89.7)
1	488 (5.5)	2 (28.6)	4 (10.3)
≥2	63 (0.7)	1 (14.3)	0 (0.0)
Time period for surgery			
1997-2002	5287 (59.1)	2 (28.6)	22 (56.4)
2003-2008	2853 (31.9)	2 (28.6)	14 (35.9)
2009-2013	807 (9.0)	3 (42.9)	3 (7.7)
Length of stay, median days (Interquartile range)	2 (1-3)	11 (3-19)	6 (3-10)

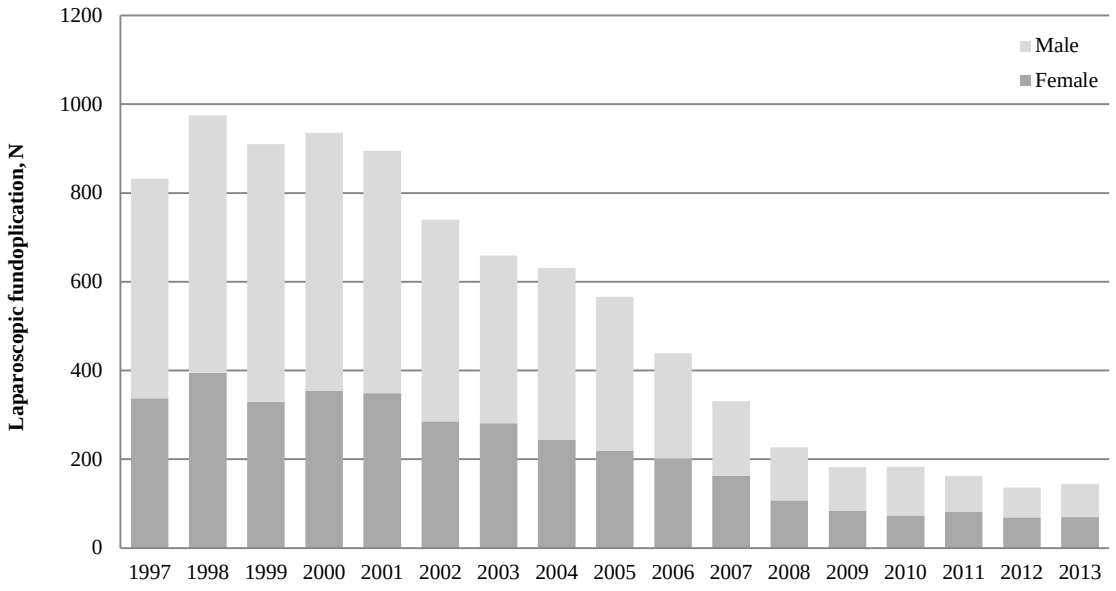
* A composite variable for quantification of general comorbid status.

Table 2. Odds ratio (OR) and 95% confidence interval (CI) of 90-day reoperation and prolonged hospital stay following laparoscopic fundoplication for gastro-oesophageal reflux disease (n=8947).

	90-day reoperation OR (95% CI) Adjusted*	**Prolonged hospital stay OR (95% CI) Adjusted***
Age at surgery	1.01 (0.98-1.04)	1.01 (1.00-1.01)
Year of surgery	1.01 (0.94-1.09)	╫
Sex		
Female	Reference	Reference
Male	0.84 (0.44-1.61)	0.76 (0.68-0.86)
Charlson score		
0	Reference	Reference
1	1.86 (0.65-5.33)	1.36 (1.04-1.66)
≥2	Not applicable	2.27 (1.30-4.00)

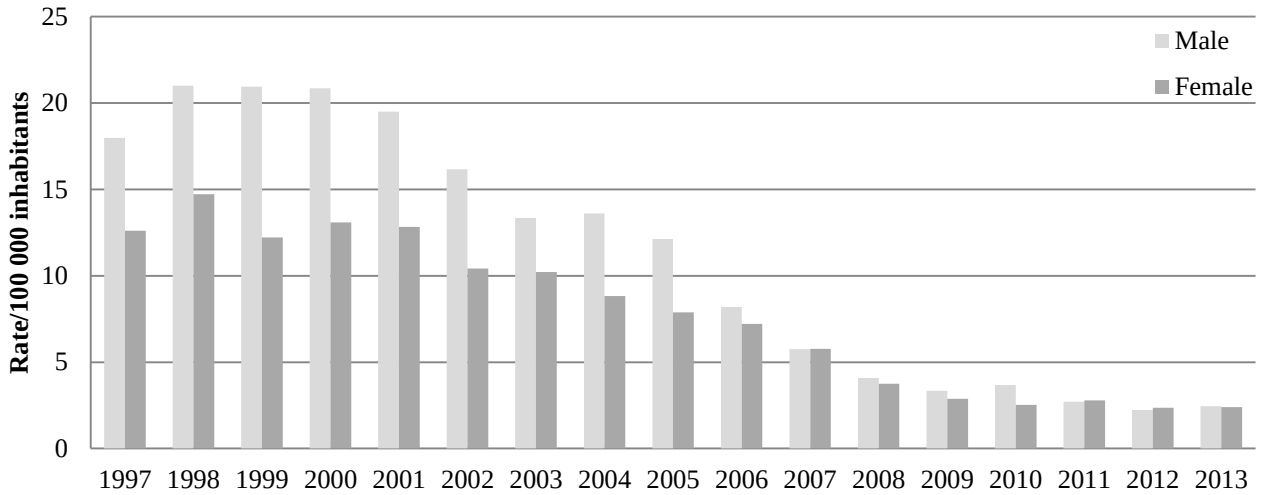
* Adjusted for sex, comorbidity score, year of surgery, and age at surgery.
╫ Adjusted by spline (approximate significance of the smooth terms: $p < 2x10^{-16}$).

Figure 1A. Laparoscopic fundoplications performed in Sweden in 1997-2013.



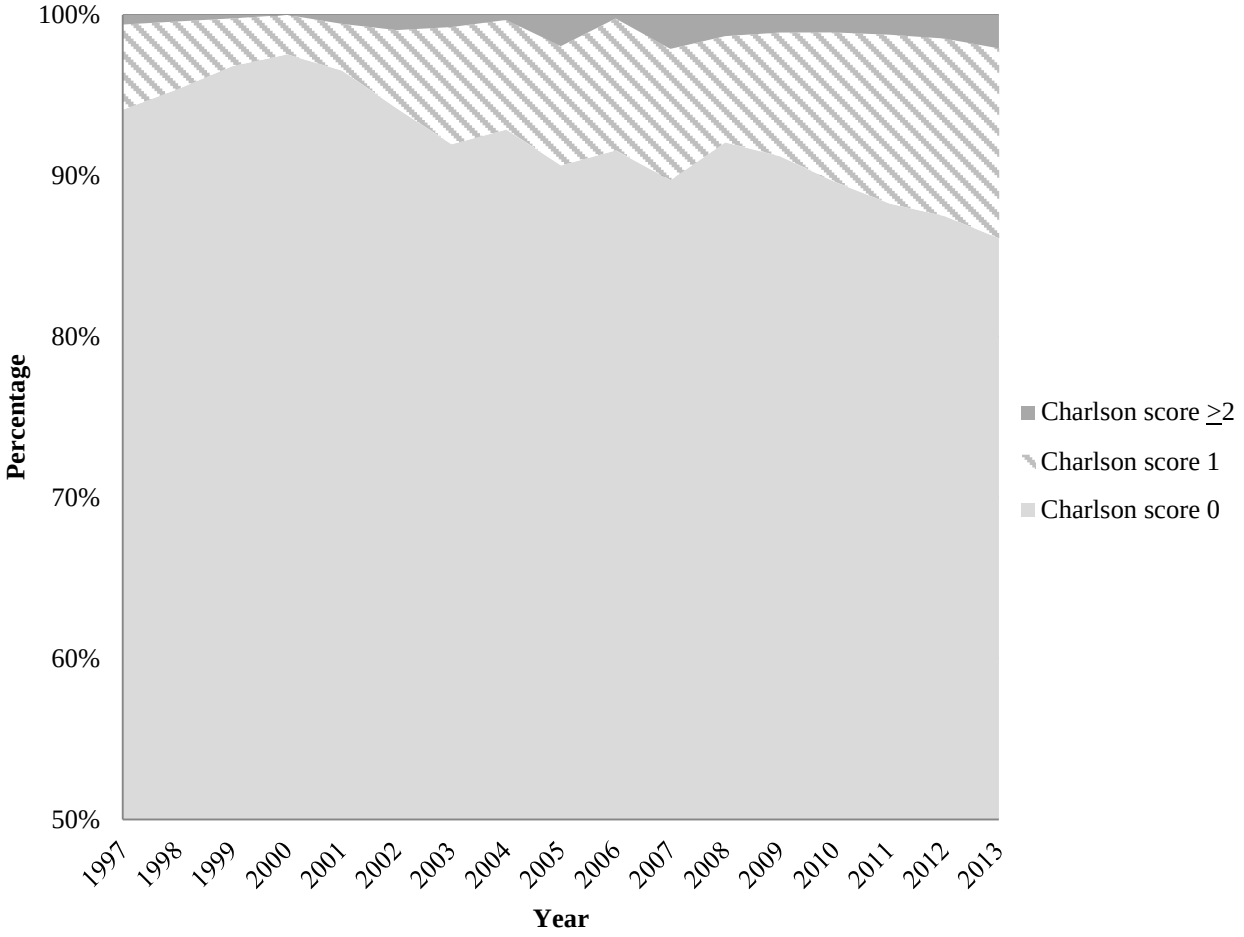
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Total, N	832	975	910	935	895	740	659	631	566	439	331	227	182	183	162	136	144
Male, N	495	580	581	581	546	455	378	387	347	237	168	120	99	110	81	67	74
(%)	(59.5)	(59.5)	(63.9)	(62.1)	(61.0)	(61.5)	(57.4)	(61.3)	(61.3)	(54.0)	(50.8)	(52.9)	(54.4)	(60.1)	(50.0)	(49.3)	(51.4)
90-day reoperation, N	3	4	2	6	2	5	3	3	3	2	2	1	1	0	0	1	1
90-day death, N	0	1	0	0	1	0	0	0	1	0	1	0	0	1	1	1	0

Figure 1B. Rate of laparoscopic fundoplications per 100 000 inhabitants.



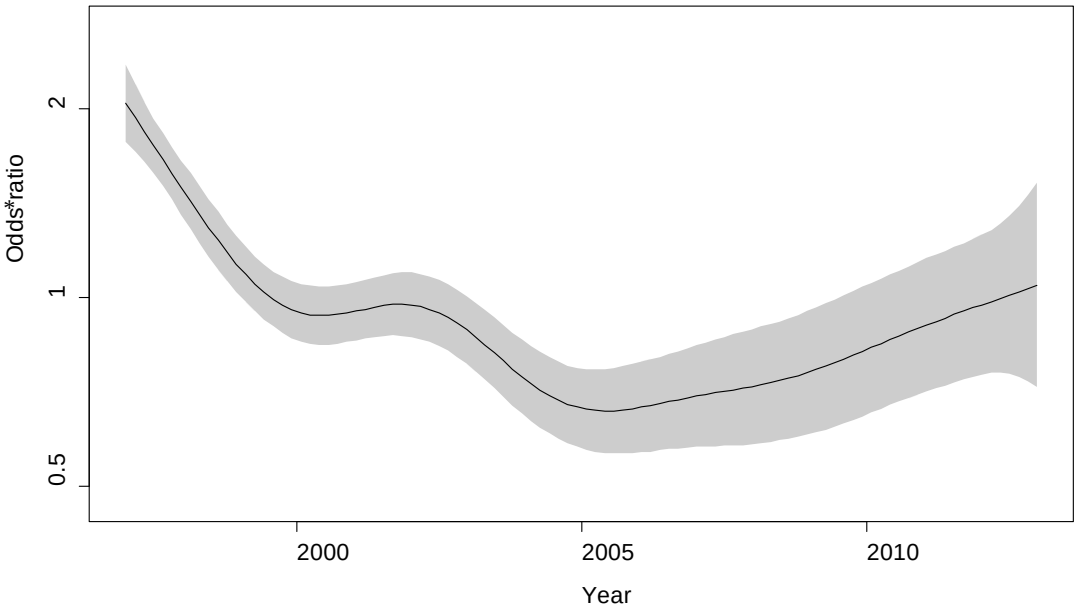
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Male rate	18.0	21.0	22.0	20.9	19.5	16.2	13.4	13.6	12.1	8.2	5.8	4.1	3.3	3.7	2.7	2.2	2.5
Female rate	12.6	14.7	12.2	13.1	12.8	10.4	10.2	8.8	7.9	7.2	5.8	3.8	2.9	2.5	2.8	2.4	2.4
Total rate	15.3	17.9	16.7	17.0	16.2	13.3	11.8	11.3	10.0	7.7	5.8	3.9	3.1	3.1	2.7	2.3	2.4

Figure 2. Distribution of comorbidity (Charlson comorbidity score)* in patients with gastro-oesophageal reflux disease who underwent laparoscopic fundoplication.



* A composite variable for quantification of general comorbid status.

Figure 3. Adjusted odds ratios (black line) with 95% confidence intervals (grey area) of prolonged hospital stay over time following laparoscopic fundoplication among patients with gastro-oesophageal reflux disease.



* Adjusted for sex, comorbidity score, and age at surgery