

BMJ Open Long-term patient satisfaction and durability of laparoscopic anti-reflux surgery in a large Danish cohort: study protocol for a retrospective cohort study with development of a novel scoring system for patient selection

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ABSTRACT

Introduction Laparoscopic anti-reflux surgery is standard of care in surgical treatment of gastro-oesophageal reflux disease and is not without risks of adverse effects, including disruption of the fundoplication and postfundoplication dysphagia, in some cases leading to reoperation. Non-surgical factors such as pre-existing anxiety or depression influence postoperative satisfaction and symptom relief. Previous studies have focused on a short-term follow-up or only certain aspects of disease, such as reoperation or postoperative quality of life. The aim of this study is to evaluate long-term patient-satisfaction and durability of laparoscopic anti-reflux surgery in a large Danish cohort using a comprehensive multimodal follow-up, and to develop a clinically applicable scoring system usable in selecting patients for anti-reflux surgery.

Methods and analysis The study is a retrospective cohort study utilising data from patient records and follow-up with patient-reported quality of life as well as registry-based data. The study population consists of all adult patients having undergone laparoscopic anti-reflux surgery at The Department of Surgery, Kolding Hospital, a part of Lillebaelt Hospital Denmark in an 11-year period. From electronic records; patient characteristics, preoperative endoscopic findings, reflux disease characteristics and details on type of surgery, will be identified. Disease-specific quality of life and dysphagia will be collected from a patient-reported follow-up. From Danish national registries, data on comorbidity, reoperative surgery, use of pharmacological anti-reflux treatment, mortality and socioeconomic factors will be included. Primary outcome of this study is treatment success at follow-up.

Ethics and dissemination Study approval has been obtained from The Danish Patient Safety Agency, The Danish Health Data Authority and Statistics Denmark, complying to Danish and EU legislation. Inclusion in the study will require informed consent from participating subjects. The results of the study will be published in peer-reviewed medical journals regardless of whether these are positive, negative or inconclusive.

Strengths and limitations of this study

- The study is a single-centre retrospective observational cohort study with prospective follow-up.
- The study is large but does not include a control group.
- Patient-reported quality of life is combined with unique national registries allowing for comprehensive follow-up.
- A combination of relevant outcomes allows for a realistic estimate of the success of anti-reflux surgery.
- Findings from this study will be used to begin development of a clinical scoring system allowing for better patient selection.

Trial registration number Clinicaltrials.gov (NCT03959020).

INTRODUCTION

Episodic reflux of gastric contents to the oesophagus is physiological but is considered gastro-oesophageal reflux disease (GORD) when accompanied by bothersome symptoms, typically heartburn, regurgitation or retrosternal pain. Extra-oesophageal symptoms such as asthma, laryngitis and chronic cough may also occur.¹ GORD is a complex and multifaceted disease.^{2–3} GORD affects 10%–20% of the Western population,⁴ and has been shown to significantly reduce the quality of life.⁵ Worldwide, the prevalence of GORD has been increasing.^{6–9}

The treatment of GORD consists of anti-secretory drugs, mainly proton pump inhibitors (PPIs), or anti-reflux surgery.¹⁰ Laparoscopic anti-reflux surgery is considered standard of care in surgical treatment of GORD,¹¹ and with careful patient selection



based on thorough preoperative workup¹²; symptom control and patient satisfaction are high compared with medical therapy.^{13 14}

Despite a tailored approach, laparoscopic anti-reflux surgery is not without risks of adverse effects, such as disruption of the fundoplication, postfundoplication dysphagia, gas-bloat syndrome and recurrence of GORD, in some cases leading to reoperation.^{15–20} Furthermore non-surgical factors such as pre-existing anxiety or depression disorders can influence postoperative satisfaction and symptom relief when compared with patients without concomitant psychological disorders.²¹

Although few studies conclude that medical and surgical treatments of GORD have similar effectiveness,^{22 23} disease-specific quality of life generally improves after anti-reflux surgery and patient satisfaction is high.¹³ Depending on type of surgical procedure, the postoperative quality of life, ranges from significantly increased compared with preoperative measurements, to values as found in subjects devoid of GERD.^{24–34} Approximately 73%–98% are satisfied with their condition after surgery and would choose surgery again.^{31–33 35–38}

Laparoscopic anti-reflux surgery is more effective than medical management with regards to short-to-medium length follow-up.^{14 39 40} Few studies provide a long-term follow-up. After 10 years, the benefits of surgery seem to decrease, but there is still a significant improvement in quality of life compared with preoperative measurements.^{41 42} Known causes of dissatisfaction are postoperative complication, redo-fundoplication and developing new symptoms such as gas-bloat and dysphagia combined with inadequate symptom relief.^{43 44}

Follow-up of randomised clinical trials has demonstrated that anti-reflux surgery patients use acid suppressing drugs, primarily PPI therapy at postoperative follow-up. However, use have been considered minimal with <20% using PPI therapy,³⁹ and 27%–44% using PPI at a 5-year follow-up.⁴⁵ A recent register-based study,⁴⁶ demonstrated a greater number of redeemed prescriptions of PPI after primary anti-reflux surgery, than previously known. Five-year, ten-year and fifteen-year risks of long-term PPI use were 29.4%, 41.1% and 56.6%, respectively. However, this register-based study could not examine whether patients had objective recurrence of reflux disease and also did not examine indication for treatment as well as position of prescribing physician.

From 2001 to 2011, 94.4% of PPI were prescribed in primary care,⁴⁷ and it is unknown why postfundoplication patients are prescribed PPI. It has previously been demonstrated that the use of acid suppressing drugs after anti-reflux surgery does not necessarily correlate with abnormal acid exposure to the oesophagus.^{48 49} In general, the use of PPI has increased rapidly in Denmark, rising 243% from 2001 to 2011 despite more restrictive guidelines and changes in reimbursement.⁴⁷ As the majority of PPIs are prescribed by general practitioners and not by the surgical centres, surgeons have very little knowledge of this aspect of life following anti-reflux surgery.

Our hypothesis is that instead of merely considering a single outcome (eg, reoperation, quality of life or use of pharmacological treatment postoperatively), a multimodal approach involving all these factors as a composite endpoint could provide a more truthful estimate of anti-reflux surgery treatment efficacy.

The aim of this study is to evaluate long-term patient satisfaction and durability of laparoscopic anti-reflux surgery in a large Danish cohort using comprehensive multimodal follow-up, and using the results of follow-up, to develop a clinically applicable scoring system usable in selecting patients for anti-reflux surgery.

METHODS AND ANALYSIS

The study is a retrospective cohort study utilising data from patient records and follow-up with patient-reported quality of life as well as registry-based data. The study was commenced on 1 March 2017 and collection of data is expected to be concluded by 1 June 2020.

Study population

The study population consists of all adult patients (age≥18) having undergone laparoscopic anti-reflux surgery (n=557) (Nomesco Classification of Surgical Procedures (NCSP)⁵⁰: KJBC01) from 1 January 2002 to 31 December 2013 in The Department of Surgery, Kolding Hospital, a part of Lillebaelt Hospital Denmark. Kolding Hospital, a part of Lillebaelt Hospital, is a tertiary surgical centre with regards to anti-reflux surgery. It is one of the two centres servicing the region of Southern Denmark and its 1.27 million inhabitants. Patients are identified through Lillebaelt Hospital's Patient Administrative System. Day of surgery will be considered index date.

Date of follow-up will be the date, patient filled out quality-of-life questionnaires as described below. For patients deceased since index date, permission to include data from electronic patient records and registry-based data has been obtained from The Danish Patient Safety Authority.

All patients will be contacted by the existing Danish national digital communication system (e-Boks) and asked them to participate in the study using an online survey. Patients exempt from using the system, will be contacted by letter with physical questionnaires. Only patients providing informed consent will be included in the study.

Data sources

Data for the study will consist of electronic patient records, follow-up with patient-reported quality-of-life measurements and registry-based data.

Electronic patient records

From the electronic patient records, the following data will be identified: age (years), sex (male/female), body mass index (kg/m²), alcohol consumption (drinks of 12 g ethanol per week), tobacco use (current, former or

never-smoker), American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI)⁵¹ and previous abdominal surgery (yes/no).

Preoperative endoscopically verified occurrence of hiatal hernia (yes/no), oesophagitis (yes/no) will be included as well as, from 24 hours pH measurement and oesophageal manometry, reflux index (%), symptom correlation (%) and presence of oesophageal motility disorder (hypomotility, normal motility or hypermotility). Patients preoperative reflux symptoms defined as typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no) are included as are surgical data included duration of surgery (minutes), type of fundoplication (270° Toupet/360° Nissen), length of hospital stay (days), perioperative and postoperative complications registered within 30 days as defined by Clavien-Dindo.⁵²

Quality-of-life follow-up

Patients will be contacted as described above and asked them to answer validated questionnaires regarding disease-specific quality of life, GERD-Health Related Quality of Life Questionnaire (GERD-HRQL)⁵³ and dysphagia (Dysphagia Handicap Index).⁵⁴ Patients will also be asked if they are currently taking PPI (yes/no), in what dosage (never/when needed/once a day/two times per day), which symptoms have warranted PPI use (reflux symptoms/dysphagia/gastritis/pre-emptive against peptic ulcer disease/other) and which physician prescribed the drug (general practitioner/surgeon/other doctor at hospital/other specialist in private practice)

Registries

All Danish inhabitants are issued with a civil registry number at birth or at date of moving to Denmark. The civil registry number is a unique personal identifier and is used across a variety of nationwide databases with regards to health, financial and educational data.⁵⁵ Data from the following nationwide Danish registries will be included in the study:

The National Patient Registry (NPR) on re-operative surgery (NCSP: KJBC00-02, KJBW96-98, KJBB00-01, KJBB96-97) and endoscopy (NCSP: KUJD02-05, KJCA55) during follow-up). NPR contains records of all discharge diagnosis since 1977 and all outpatient diagnosis since 1994.^{56 57} All performed procedures, including endoscopies and surgeries, are also registered using NCSP.

The National Patient Registry of Psychiatry (NPR-PSYK) on psychiatric diagnoses (ICD-10: F01-F99) in a 2-year period before primary surgery. NPR-PSYK is a sub-registry of NPR and specifically contains records of all psychiatric discharge and outpatient diagnosis from psychiatric departments since 1995.^{56 57}

The Civil Registry on marital status, 90-day mortality after primary surgery and all-cause mortality during follow-up. The Danish Civil Registry maintains complete records of births, deaths, civic status and emigration status of the entire Danish population based on civil registration number.⁵⁸

The Danish National Prescription Registry on use of anti-reflux medication (ATC: A02BA, A02BC, A02BX), anti-thrombotic treatment (ATC: B01A), non-steroid anti-inflammatory drugs (NSAID) (ATC: M01A) and selective serotonin reuptake inhibitors (SSRI) (ATC: N06AB) in a time period beginning 2 years before surgery and ending at end of follow-up. The Danish National Prescription Registry contains information on all sale of prescription drugs including date of sale, Anatomical Therapeutic Chemical (ATC) Classification code, civil registration number of buyer and package volume since 1994.⁵⁹

Statistics Denmark on educational level at time of primary surgery⁶⁰ defined by the International Standard Classification of Education (ISCED),⁶¹ occupation status (employed/unemployed/retired)⁶² and equivalent annual income in the year preceding primary surgery.⁶³

Primary outcome

Primary outcome of the study is treatment success or failure, with failure defined for each patient as at least one of the following statements being fulfilled:

1. Having undergone reoperation (NSCP: KJBC00-02, KJBW96-98, KJBB00-01, KJBB96-97) between index date and end of follow-up.
2. Having filled prescription of >60 defined daily dosages (DDD) per year of PPI redeemed using no less than two scripts in any year between index date and end of follow-up.
3. Having no measure ≥ 3 on GERD-HRQL indicating symptoms being bothersome every day.
4. Having no measure ≥ 4 on Dysphagia Handicap index indicating symptoms being a moderate problem.

Date of failure will be defined as follows: In case of (1), date of failure will be date of reoperation. In case of (2), date of failure will be date of first prescription filled in the year, where >60 DDD of PPI are filled with at least two scripts. In case of (3) or (4), date of failure will be end of follow-up.

Secondary outcomes

Secondary outcome will be 90-day mortality after primary surgery, rate of reoperation, use of PPI in DDD/year, use of PPI at follow-up (including indication and prescribing physician) and quality of life defined by GERD HRQL, Dysphagia Handicap Index. As a secondary outcome, concordance between failures defined only be register-based data and failures based on quality-of-life data will be examined.

Statistical analysis

Contingency tables

Contingency tables will be created listing:

1. Patient characteristics: Age (median), sex (male/female), body mass index (kg/m^2), alcohol consumption (drinks of 12g ethanol per week), tobacco use (current, former or never-smoker), ASA score, CCI, preoperative psychiatric diagnoses, use of anti-reflux medication (yes/no), and ulcerogenic medication

before surgery (yes/no) and previous abdominal surgery (yes/no), educational level at time of primary surgery (ISCED), occupation status (employed/unemployed/retired) and equivalent annual income in the year preceding primary surgery.

2. GORD characteristics: Symptom profile: typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no), endoscopically verified occurrence of hiatal hernia (yes/no), oesophagitis (yes/no), measures from 24 hours pH measurement and oesophageal manometry: reflux index (%), symptom correlation (%) and presence of oesophageal motility disorder (hypomotility, normal motility or hypermotility).
3. Operative characteristics: Duration of surgery (minutes), type of fundoplication (270° Toupet/360° Nissen), length of hospital stay (days), perioperative and postoperative complications registered within 30 days as defined by Clavien-Dindo and 90-day mortality.
4. Follow-up: Rate of reoperation (%), use of PPI in DDD/year, use of PPI at follow-up (including indication and prescribing physician), GERD-HRQL and Dysphagia Handicap Index.

Categorical and continuous variables will be compared using χ^2 , Fisher's Exact test and Kruskal-Wallis test where appropriate, including when comparing secondary outcomes between patients defined as having treatment failure and treatment success. Included patients with missing data from explanatory variables will be omitted from the study.

Cox regression

Cox regression will be performed with treatment success as dependent variable, time to end of follow-up (as defined above) and the following variables will be tested and included as independent variables where appropriate: Age (median), sex (male/female), body mass index (kg/m²), alcohol consumption (drinks of 12 g ethanol per week), tobacco use (current, former or never-smoker), ASA score, CCI, preoperative psychiatric diagnoses, use of anti-reflux medication (yes/no), and ulcerogenic medication before surgery (yes/no) and previous abdominal surgery (yes/no), educational level at time of primary surgery (ISCED), occupation status (employed/unemployed/retired) and equivalent annual income in the year preceding primary surgery, typical symptoms (yes/no), atypical symptoms (yes/no) and dysphagia (yes/no), endoscopically verified occurrence of hiatal hernia (yes/no), oesophagitis (yes/no), measures from 24 hours pH-measurement and oesophageal manometry: reflux index (%), symptom correlation (%) and presence of oesophageal motility disorder (hypomotility, normal motility or hypermotility), type of fundoplication (270° Toupet/360° Nissen).

Proportional hazards assumption will be tested and reported appropriately. Interactions between all included covariates will be investigated and included as interaction terms in the regression analysis if statistically significant.

Clinical scoring system

Using results from the Cox regression and using the methods for validation described by Steyerberg and Vergouwe,⁶⁴ a clinical scoring system will be developed with the purpose of identifying probability of treatment success based on preoperative known variables. The scoring system will be internally validated using bootstrap resampling. External validation will be the subject of future studies.

Power calculation

Previous studies have shown a reoperation rate of 5% after anti-reflux surgery in Denmark⁶⁵ and a long-term PPI use of 38.5%.⁴⁶ Pilot data from our study show that some patients undergo reoperation without long-term PPI use and therefore we assume a composite failure rate of 40%.

For Cox regression analysis, assuming a loss to follow-up leaving 450 patients for analysis, a failure event rate in the study population of 40%, significance level of 0.05 and power of 0.9, the estimated effect size and coefficient demonstrated will be -0.4832.

Data management

Data collected from electronic patient records and patient-reported quality-of-life follow-up will be stored using RedCAP (REDCap 7.4.23, Vanderbilt University, Nashville, Tennessee, USA) hosted by OPEN—Open Patient Data Explorative Network, Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Denmark. Data will be transferred to Statistics Denmark and merged with registry data. All analysis will be performed using STATA V.15 (StataCorp, College Station, Texas, USA) on the servers of Statistics Denmark.

Patient and public involvement statement

The hypothesis of this study was conceived with the help of patients through outpatient clinical follow-up after anti-reflux surgery. Through patient experience of the different postoperative consequences and complications, this study's composite endpoint involves both reoperation, pharmacological treatment and quality of life.

Patient participation is essential in this follow-up study but does not affect the conduct of the study. Time required for participation has been evaluated by a small sample of patients and was considered minimal.

All patient eligible for inclusion in the study, are offered to be informed of the results, whether they participate or not. The results and their consequence for future patient selection, will be disseminated to the public through media.

ETHICS AND DISSEMINATION

Permission to contact patient for the project has been obtained from The Danish Patient Safety Agency. Each patient must consent to inclusion in the study, including the use of electronic patient records and registry-based data as described above. For deceased patients, permission for use of electronic patient records and registry-based

data has been obtained from The Danish Patient Safety Agency. Specific permission for use of registry-based data has been obtained from The Danish Health Data Authority and Statistics Denmark.

The results of the study will be published in peer-reviewed medical journals regardless of whether these are positive, negative or inconclusive. Two peer-reviewed articles are expected to come from this study: one including the primary results, and another calculating a clinical scoring system based on the results.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study has been approved and registered at Lillebaelt Hospital according to current Danish Law and has previously been approved by The Danish Data Protection Agency (Permission #17/1942). Generated datasets will be stored on the servers of Statistics Denmark in compliance with Danish and EU regulations on personal health data and will be anonymised after merging, so that the unique personal identifier is removed.

Provenance and peer review Not commissioned; externally peer reviewed.

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