Title: HOSPITAL VOLUME OF ANTI-REFLUX SURGERY IN RELATION TO ENDOSCOPIC AND SURGICAL RE-INTERVENTIONS

Running head: Hospital volume of anti-reflux surgery

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MINI-ABSTRACT

33,060 patients received anti-reflux surgery; frequencies of 30-day re-intervention, endoscopic re-intervention and secondary anti-reflux surgery were 1.2%, 4.6% and 7.0%, respectively. Higher hospital volume for anti-reflux surgery did not decrease the risk of re-interventions, but rather increased risk estimates.

ABSTRACT

Objective: To test the hypothesis that higher hospital volume decreases endoscopic and surgical re-intervention rates following anti-reflux surgery.

Background: Anti-reflux surgery for gastro-esophageal reflux disease (GERD) is followed by varying rates of re-interventions. Whether hospital volume influences re-intervention rates is uncertain.

Methods: This population-based cohort study used nationwide data from Denmark, Finland and Sweden for patients having undergone primary anti-reflux surgery. Hospitals were divided into tertiles based upon annual volume, i.e. three equal sized groups. The outcomes were 30-day surgical re-intervention, endoscopic re-intervention and secondary anti-reflux surgery. Multivariable Cox regression provided hazard ratios (HRs) with 95% confidence intervals (CIs) for risk of the first outcome occurrence. Incidence rate ratios (IRRs) were calculated to count all outcome occurrences. All risk estimates were adjusted for age, sex, comorbidity, type of anti-reflux surgery, year of surgery and country.

Results: Among 33,060 patients and a median follow-up of 12 years after anti-reflux surgery, the frequencies of 30-day re-intervention, endoscopic re-intervention and secondary anti-reflux surgery were 1.2%, 4.6% and 7.0%, respectively. When comparing the highest with the lowest tertiles, higher hospital volume did not decrease HRs of 30-day re-intervention (adjusted HR=1.14, 95% CI 0.73-1.77), endoscopic re-intervention (HR=1.21, 95% CI 0.96–1.51) or secondary anti-reflux surgery (HR=1.28, 95% CI 1.05–1.54), but rather increased point estimates. The IRRs showed similar patterns.

Conclusions: Higher hospital volume of primary anti-reflux surgery may not decrease risk of endoscopic or surgical re-intervention, suggesting that centralization will not decrease rates of postoperative complications or recurrence of GERD.

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INTRODUCTION

Anti-reflux surgery is an effective treatment of severe gastro-esophageal reflux disease (GERD),[1-4] but carries a risk of serious complications[5] and a high rate of recurrent GERD. The reported rates of recurrence of GERD have been varying, with some institutional cohort studies suggesting rates of approximately 40%,[6,7] whereas our recent Swedish population-based cohort study found a lower rate of 17.7%,[8] and our population-based cohort study from England identified a higher rate of 62.7%.[9] These data indicate a need for improving anti-reflux surgery to reduce complications and GERD recurrences. One such possibility could be centralisation to fewer centres with special interest and experience in these procedures. Complications and recurrence of GERD after anti-reflux surgery often require endoscopic or surgical re-intervention. In an English study, low hospital volume was associated with an increased risk of surgical re-intervention (hazard ratio (HR) 1.32, 95% confidence interval (CI) 1.04–1.67),[9] while a previous Swedish study did not find any statistically significant increase (HR 1.09, 95% CI 0.77-1.53).[8] Otherwise, little research has examined the role of hospital volume of anti-reflux surgery in relation to postoperative re-interventions. Because of the scarcity of studies, the partly contradictory findings and the clinical relevance of the topic, this study aimed to help clarify whether higher hospital volume of anti-reflux surgery reduces the need for short-term and long-term postoperative endoscopic or surgical re-interventions. The study focused on endoscopic and surgical re-interventions, and not medical intervention, because the widespread use of medication with proton pump inhibitors for various indications or without clear indications prohibited a valid assessment of medical re-intervention after anti-reflux surgery.

METHODS

Design

This multinational and population-based cohort study was based on information from nationwide health data registries from the three Nordic countries Denmark, Finland and Sweden. The source cohort, entitled the Nordic Antireflux Surgery Cohort (NordASCo), has been described in detail in a separate publication.[10] All participants had a recorded diagnosis of GERD when they were 18 years or older, and among these, all who had undergone anti-reflux surgery were considered for inclusion into the present study. Excluded were patients with a diagnosis of esophageal cancer or achalasia, as well as patients with a primary diagnosis of giant para-esophageal hernia as the indication for surgery. The study periods varied in different countries depending on the years of initiation of registries and data retrieval; Denmark (1996 to 2014), Finland (1997 to 2014) and Sweden (1997 to 2013). The similar structure of the nationwide health data registries in the Nordic countries and the use of personal identity codes of each resident in these countries enabled linkages of individual information among registries.[10] National guidelines for the diagnosis and preoperative workup for GERD were established prior to the study, however did evolve during the study period, limiting heterogeneity in regional practice. All required ethical and data permissions were retrieved from the relevant authorities within each country.[11]

Exposure

The exposure under investigation was hospital volume of primary anti-reflux surgery. The number of hospital in each country performing anti-reflux surgery was 36 in Denmark, 61 in Finland, and 75 in Sweden. To account for temporary fluctuations in

annual hospital volume between single calendar years and to incorporate the experience achieved during the last few years prior to each operation, hospital volume was calculated using a 4-year moving average number of operations at each hospital, including the year of surgery and also the 3 years before. For patients entering the cohort less than 4 years before surgery, the moving average was calculated based on the available amount of years before the surgery. The hospital volume variable was divided by tertiles, i.e. three groups of about equal number of patients operated per year over an assessment period of up to 4 years.

Outcomes

Three outcomes were examined:

1. Re-intervention within 30 days of primary anti-reflux surgery, as defined by any of the surgical or endoscopic re-interventions listed in appendix A.
2. Endoscopic re-intervention during the entire follow-up period after primary anti-reflux surgery.
3. Secondary anti-reflux surgery during the entire follow-up period after primary anti-reflux surgery.

The outcomes are defined in more detail in appendix A.

Confounders

Six variables were considered potential confounders: 1) age (continuous), 2) sex (male or female), 3) comorbidity (Charlson comorbidity index 0, 1, or ≥2),[12] 4) type of anti-reflux surgery (open, laparoscopic or both), 5) year of anti-reflux surgery (1996-2005 or 2006-2014, to divide the study period into two approximately equally long periods)

and 6) country (Finland, Denmark, or Sweden). Previous studies have identified the importance of these confounders in clinical outcome following anti-reflux surgery.[8,9]

Statistical analysis

The statistical analysis included two approaches to evaluate the influence of hospital volume on the risk of endoscopic or surgical re-intervention outcomes. First, multivariable Cox regression was used to calculate HRs with 95% CIs. Person-years were counted from the date of primary anti-reflux surgery until date of any of the first outcome, death, or end of follow-up, whichever came first.

Second, to account for repeated occurrence of the outcomes, incidence rate ratios (IRRs) with 95% Cis were calculated with the negative binomial regression model. Exposure time was calculated from the date of anti-reflux surgery until death or end of follow-up, whichever came first. In this approach, all outcome occurrences were counted independent of the occurrence of any previous outcome.

All risk estimates in both statistical approaches were adjusted for the six confounders presented above with the same categorization. The correlation between the confounders was checked computing the coefficient of correlation rho for categorical variables and the Pearson's coefficient of correlation for the continuous variables. The absolute values of the correlation coefficients were all well below the cut-off of 0.4 (maximum absolute coefficient 0.24).[13] To account for possible differences in results for the three countries, interaction terms between the exposure and country were computed and stratified analyses where reported because the interaction terms were significant for all the outcomes and models with the exception of 30-day re-intervention.

An experienced biostatistician (GS) conducted the data management and statistical analyses according to a pre-defined study protocol, using the statistical software STATA/MP (version 15.1).

RESULTS

Patients

The study included 33,060 patients who underwent anti-reflux surgery for GERD during the study period (4,149 from Denmark, 17,180 from Finland and 11,731 from Sweden). Table 1 describes patient characteristics of the study participants. The average age was 50.1 years, 54.2% (n=17,914 patients) were male, and 85.0% (n=28,112) had a Charlson comorbidity index score of 0. The average hospital volume was 12.3 cases per year, and with hospitals divided into tertiles, i.e. three about equal sized groups, the annual number of cases was <8, 8-20 and ≥21. The distribution of hospital volume of anti-reflux surgery by country is presented in Figure 1. The 30-day re-intervention rate was 1.2% (n=396), the rate of repeat endoscopic re-intervention during the entire follow-up was 4.6% (n=1,537) and the rate of secondary anti-reflux surgery during the entire follow-up was 7.0% (n=2,311). The percentage of people free from complications over time after anti-reflux surgery is presented in Figure 2.

Hospital volume and risk of endoscopic or surgical re-intervention

The Cox regression analysis revealed no decrease in the adjusted HRs with higher hospital volume for any of the three re-intervention outcomes (Table 2). Comparing the highest with the lowest tertiles of hospital volume, the HR of 30-day re-intervention was 1.14 (95% CI 0.73-1.77) and that for interventional endoscopy was 1.21 (95% CI 0.96-1.51). Higher hospital volume was even associated with a statistically significantly increased HR of secondary anti-reflux surgery (HR 1.28, 95% CI 1.05-1.54), when comparing the highest with the lowest tertiles of hospital volume (Table 2).

In the approach where all outcome occurrences were counted, the adjusted IRRs showed a similar trend, i.e. no decreased risk estimates with higher hospital volume, but rather the opposite (Table 3). Comparing the highest with the lowest tertiles of hospital volume, all point estimates were increased, and the IRR for secondary anti-reflux surgery was statistically significantly increased (IRR 1.27, 95% CI 1.03-1.56).

Separate analysis by the three individual countries showed no decrease in HRs or IRRs of endoscopic or surgical re-interventions associated with increasing hospital volume (Supplementary Table 1).

DISCUSSION

This cohort study found low rates of endoscopic and surgical re-interventions after primary anti-reflux surgery in Denmark, Finland and Sweden. Against the hypothesis, higher hospital volume was not associated with any decrease in re-interventions, but rather an increase in secondary anti-reflux surgery.

Strengths of the study include the population-based design mirroring unselected clinical practice, the large sample size from three entire countries providing a sufficient statistical power, and the complete follow-up of all study participants prohibiting loss to follow-up. In addition, the data were of high quality and validity regarding hospital volume of anti-reflux surgery, endoscopic and surgical re-interventions and the potential confounders included in the models. Yet, the study also has limitations. Firstly, because the combination of Nordic registry data required substantial time and expertise from experienced collaborators in all countries,[10] we were not able to use data from the most recent years (after 2014). Secondly, the level of technical complexity of the primary anti-reflux surgery could not be accounted for, except for excluding giant para-esophageal hernia procedures. Additional factors may have complicated the surgery, including e.g. obesity and adhesions from other surgery. Thirdly, despite the several variables adjusted for, confounding from other factors cannot be excluded, e.g. the degree of GERD that initiated the primary surgery. Fourthly, we did not have data pertaining to specific variations in anti-reflux surgery, however the most commonly performed procedures are Nissen and Toupet fundoplication within the countries included. Finally, the method of clinical follow-up

after primary anti-reflux surgery in the different hospitals was not possible to capture, a factor that might have influenced to the endoscopic or surgical re-intervention rates.

The two statistical approaches utilized complemented each other. The HRs estimated the risk of the first of any of the outcomes, thus dismissing any later outcome events. The IRRs included all the information available regarding the outcome by counting all the events a person experienced within the study. While one method assessed the hazard of having the event, the other studied the frequency of the event. The fact that the HRs and IRRs showed similar patterns validates the findings. The only statistically significant association that remained in both statistical approaches was that higher hospital volume was associated with an increased risk of secondary anti-reflux surgery, possibly related to patient selection between centres.

The lack of decreased rates of endoscopic or surgical re-interventions with higher hospital procedural volume was unexpected. This contrasts research in major complex surgery that has established increasing hospital procedural volume leads to improved clinical outcomes.[14-16] The rather opposite associations in the present study may suggest that there is a difference in the clinical follow-up of patients and in the threshold for re-interventions in higher volume centres compared to those of lower volume. Compared to primary anti-reflux surgery, secondary anti-reflux surgery is more technically challenging and carries a higher complication rate, including esophageal perforation, and thus preferentially may be undertaken by high-volume surgeons.[17] It is possible that recurrences of GERD after anti-reflux surgery are more often treated medically in hospitals of lower annual volume compared to in higher

volume centres. This explanation was not possible to assess in the present study. Future investigations will need prospectively collected data to assess how hospital volume influences long-term functional outcomes and health-related quality of life after anti-reflux surgery.

Previous studies examining the influence of hospital volume upon surgical outcomes have shown complex interventions requiring good intensive care support do benefit from centralization to high-volume centers.[18,19] However, although primary anti-reflux surgery is a technical procedure it is a less traumatic, and followed by a low risk of severe complications and little need for advanced perioperative care. This surgery may thus be less influenced by hospital volume and possibly more influenced by individual surgeon volume or experience. Therefore, future research assessing surgery volume of anti-reflux surgery in relation to postoperative outcomes should examine the role of the individual surgeon. Except for investigating annual surgeon volume, research using video analysis and specifically observed clinical human reliability analysis (OCHRA) may help identify sources of technical errors intra-operatively that are associated with poor outcomes, requiring surgical or endoscopic re-intervention and recurrence of GORD symptoms.[20-22]

In conclusion, this population-based cohort study from three entire Nordic countries indicates that increasing hospital volume of primary anti-reflux surgery study is not associated with any decrease in endoscopic or surgical re-interventions in the short or long-term postoperative perspective. Instead, centres with higher annual volumes had an increase in secondary anti-reflux surgery, which may speculatively be secondary to

increased vigilance for recurrent symptoms and a lower threshold for surgical re-
2 interventions. Research examining the role of the individual surgeon volume and technique may lead to improvements in the future surgical treatment of GERD.

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Table 1. Characteristics of study participants having undergone anti-reflux surgery.

	All patients Number (%)	Patients without re-interventions Number (%)	Patients with re-interventions Number (%)
	33060	29628 (89.6%)	3432 (10.4%)
Age (years) (±SD)	50.1 (±13.2)	50.1 (±13.2)	50.1 (±13.2)
Sex			
Men	17914 (54.2%)	16273 (54.9%)	1641 (47.8%)
Women	15146 (45.8%)	13355 (45.1%)	1791 (52.2%)
Charlson comorbidity score			
0	28112 (85.0%)	25264 (85.3%)	2848 (83.0%)
1	4118 (12.5%)	3650 (12.3%)	468 (13.6%)
≥2	830 (2.5%)	714 (2.4%)	116 (3.4%)
Type of surgery			
Open	4580 (13.8%)	4176 (14.1%)	404 (11.8%)
Laparoscopic	28258 (84.5%)	25252 (85.2%)	3005 (87.6%)
Converted	222 (0.7%)	199 (0.7%)	23 (0.7%)
Year of surgery			
1996-2005	22424 (67.8%)	20019 (67.6%)	2405 (70.1%)
2006-2014	10636 (32.2%)	9609 (32.4%)	1027 (29.9%)
Country			
Denmark	4149 (12.6%)	3445 (11.6%)	704 (20.5%)
Finland	17180 (52.0%)	15634 (52.8%)	1546 (45.1%)
Sweden	11731 (35.4%)	10549 (35.6%)	1182 (34.4%)
Hospital volume per year (IQR)*	12.3 (5.3-26.3)	12.3 (5.5-26.7)	21.3 (10.8-36.0)
<8	2022 (6.1%)	1847 (6.2%)	175 (5.1%)
8-20	6843 (20.7%)	6213 (21.0%)	630 (18.4%)
≥21	24195 (73.2%)	21568 (72.8%)	2627 (76.5%)
Re-intervention by year after primary surgery			
≤1	-	-	1443 (42.0%)
>1-2	-	-	547 (15.9%)
>2-5	-	-	712 (20.8%)
>5	-	-	730 (21.3%)
Death during follow-up	2532 (7.7%)	2241 (7.6%)	291 (8.5%)
Re-intervention			
30-day re-intervention	-	-	396 (11.5%)
Endoscopic re-intervention	-	-	1537 (44.8%)
Secondary anti-reflux surgery	-	-	2311 (67.3%)

* Hospital volume per year was calculated as a moving average of the 4 years before
2 the patient's surgery date. SD – Standard deviation; IQR – Inter-Quartile Range

Table 2. Hazard ratios (HR) and 95% confidence interval (CI) of re-interventions after anti-reflux surgery for different levels of hospital volume.

	Model 1	Model 2	Model 3
Volume (tertiles)*	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	30-day re-intervention		
Lowest	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	1.23 (0.77-1.96)	1.22 (0.77-1.96)	1.31 (0.782-2.10)
Highest	1.07 (0.69-1.65)	1.06 (0.69-1.64)	1.14 (0.73-1.77)
	Endoscopic re-intervention		
Lowest	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	1.10 (0.86-1.40)	1.10 (0.86-1.40)	1.22 (0.96-1.56)
Highest	1.08 (0.86-1.35)	1.08 (0.87-1.36)	1.21 (0.96-1.51)
	Secondary anti-reflux surgery		
Lowest	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	0.92 (0.75-1.13)	0.91 (0.74-1.12)	0.99 (0.80-1.21)
Highest	1.17 (0.97-1.41)	1.16 (0.96-1.40)	1.28 (1.05-1.54)

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Adjusted for age and sex, Charlson comorbidity score, type of surgery, year of surgery, and country.

* Number of primary anti-reflux procedures per tertile: Lowest: <8; intermediate: 8-20; highest: ≥21.

Table 3. Incidence rate ratios (IRR) and 95% confidence interval (CI) of re-interventions after anti-reflux surgery for different levels of hospital volume.

		Model 1	Model 2	Model 3
Outcome	**Incidence rate/10,000 (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
	30-day re-intervention			
Lowest	4.41 (3.03-6.43)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	5.34 (4.44-6.44)	1.28 (0.77-2.11)	1.25 (0.80-1.96)	1.28 (0.82-1.97)
Highest	4.36 (3.91-4.86)	1.12 (0.70-1.79)	1.09 (0.72-1.66)	1.04 (0.69-1.56)
	Endoscopic re-intervention			
Lowest	0.30 (0.26-0.34)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	0.30 (0.28-0.32)	1.40 (0.83-2.38)	1.33 (0.80-2.19)	1.18 (0.80-1.74)
Highest	0.26 (0.25-0.27)	1.61 (0.97-2.68)	1.57 (0.94-2.62)	1.28 (0.86-1.90)
	Secondary anti-reflux surgery			
Lowest	0.20 (0.17-0.24)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Intermediate	0.19 (0.17-0.21)	0.98 (0.74-1.30)	0.97 (0.73-1.28)	1.02 (0.81-1.28)
Highest	0.23 (0.22-0.24)	1.33 (1.02-1.73)	1.32 (1.02-1.70)	1.27 (1.03-1.56)

Model 1: Unadjusted
Model 2: Adjusted for age and sex
Model 3: Adjusted for age and sex, Charlson comorbidity score, type of surgery, year of surgery, and country.
Model 1 to 3: Results from negative binomial regression
* Number of primary anti-reflux procedures per tertile: Lowest: <8; intermediate: 8-20; highest: ≥21.

FIGURE LEGENDS

Figure 1. Distribution of hospital volume of anti-reflux surgery by country.

Figure 2. Percentage of people free from endoscopic or surgical re-interventions over time after anti-reflux surgery.