




# A Nationwide Cohort Study of Outcome after Pediatric Appendicitis

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## Abstract

**Introduction** Children with appendicitis often present with complicated disease. The aim of this study was to describe the clinical management of pediatric appendicitis, and to report how disease severity and operative modality are associated with short- and long-term risks of adverse outcome.

**Materials and Methods** A nationwide retrospective cohort study of all Swedish children (<18 years) diagnosed with appendicitis, 2001 to 2014 ( $n = 38,939$ ). Primary and secondary outcomes were length of stay, surgical site infections, readmissions, 30-day mortality, and long-term risk of surgery for small bowel obstruction (SBO). Implications of complicated disease and operative modality were assessed with adjustment for age, gender, and trends over time.

**Results** Complicated appendicitis was associated with longer hospital stay (4 vs. 2 days,  $p < 0.001$ ), increased risk of surgical site infection (5.9 vs. 2.3%, adjusted odds ratio [aOR]: 2.64 [95% confidence interval, CI: 2.18–3.18],  $p < 0.001$ ), readmission (5.5 vs. 1.2, aOR: 4.74 [95% CI: 4.08–5.53],  $p < 0.001$ ), as well as long-term risk of surgery for SBO (0.7 vs. 0.2%, adjusted hazard ratio [aHR]: 3.89 [95% CI: 2.61–5.78],  $p < 0.001$ ). Intended laparoscopic approach was associated with reduced risk of surgical site infections (2.3 vs. 3.1%, aOR: 0.74 [95% CI: 0.62–0.89],  $p = 0.001$ ), but no overall reduction in risk for SBO; however, successful laparoscopic appendectomy was associated with less SBO during follow-up compared with open appendectomy (aHR: 0.27 [95% CI: 0.11–0.63],  $p = 0.002$ ).

**Conclusion** Children treated for complicated appendicitis are at risk of substantial short- and long-term morbidities. Fewer surgical site infections were seen after intended laparoscopic appendectomy, compared with open appendectomy, also when converted procedures were accounted for.

## Keywords

- ▶ pediatric appendicitis
- ▶ complications
- ▶ surgical site infection
- ▶ small bowel obstruction
- ▶ laparoscopic

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## Introduction

Appendicitis is the most common cause of abdominal surgery in children, accounting for significant burden of disease and related costs.<sup>1–3</sup> Perforation rates are considerable in the younger children, yet the outcome from appendicitis has improved with better diagnostics, effective perioperative care and safer anesthesia, and surgery.<sup>4,5</sup> Nonetheless, even for children in health care systems that provide high access and low thresholds to emergency health care, every four to six children with appendicitis will develop a complicated course of disease with perforation, peritonitis, or abscess.<sup>6–9</sup>

More severe appendicitis is associated with longer hospital stay, more surgical adverse events, and higher costs.<sup>5</sup> An increased risk of small bowel obstruction (SBO) has been reported in adults diagnosed with complicated as compared with uncomplicated appendicitis (1.5 vs. 0.5% risk during 10 years of follow-up,<sup>10</sup> and 2.8 vs. 0.7% during 30 years of follow-up<sup>11</sup>). The few single-center studies on pediatric appendicitis that have been performed are in line with these results<sup>12,13</sup>; however, comprehensive population-based analyses of the short- and long-term risks for adverse outcome in complicated and uncomplicated pediatric appendicitis are needed. Besides single-center studies, there is a lack of evidence from European settings that the ascendance of laparoscopic surgery for pediatric appendicitis has influenced these risks.<sup>14</sup>

The aim of this study was to describe the management of appendicitis in a national cohort of children, and to assess how appendicitis severity and the use of laparoscopic surgery correlated with length of stay and the risk of short- and long-term adverse events, including readmissions, surgical site infections, mortality, and long-term risk for SBO.

## Materials and Methods

### Study Design and Setting

This was a register-based observational cohort study of all cases of acute pediatric appendicitis in Sweden during a period of 14 years (January 1, 2001, to December 31, 2014). Children treated for appendicitis at any time during the study period were followed up in health care registers until migration or to December 31, 2014. During the study period, the number of hospitals performing pediatric appendectomies in Sweden decreased, as were the caseload volume for most of them, following the general trend of centralizing pediatric surgical care. In 2014, 7 university hospitals and another 44 regional or local hospitals performed pediatric appendectomies.<sup>7</sup>

### Inclusion and Exclusion Criteria

Eligible for inclusion were all Swedish children younger than 18 years, admitted for a first episode of appendicitis. Exclusion criteria included elective surgery and cases with ambiguous coding ([–Supplementary Table S1](#), available in the online version).

### Data Sources and Data Collection

The National Patient Register provides complete coverage of all inpatient care in Sweden, and records of patients eligible

for inclusion were retrieved from this register.<sup>15</sup> Patient-level information about mortality and prescription of antibiotics were retrieved from the Swedish Cause of Death Register and the Swedish Prescribed Drug Register (available from 2006).

### Outcome Variables

Outcome variables were length of stay from admission to discharge, 30-day surgical site infection rate, readmission rate and mortality rate, and long-term risk of SBO. Surgical site infection was defined either by International Classification of Diseases, Version 10 (ICD-10) code T81.4 (infection related to surgical intervention) or prescription of  $\beta$ -lactamases stable penicillin or lincosamides within 30 days from discharge (details presented in [–Supplementary Table S2](#), available in the online version). Readmission was defined as a new episode of inpatient care, related to appendicitis or due to any abdominal surgery within 30 days from discharge ([–Supplementary Table S3](#), available in the online version). SBO was defined by any of ICD-10 codes K56.0, K56.5, K56.7, or K91.3, combined with abdominal surgery, occurring 30 days or later from the date of the appendicitis (median follow-up 7.4 years) ([–Supplementary Table S3](#), available in the online version).

### Primary Exposures and Potential Confounders

Primary exposures were type of appendicitis and type of clinical treatment. Type of appendicitis was categorized using the ICD-10 as either complicated (K35.0–K35.2, i.e., appendicitis with generalized peritonitis or appendicitis abscess) or uncomplicated disease (K35.3–K37.9, i.e., other forms of acute appendicitis). The diagnosis was determined by the surgeon in charge at the appendectomy, or by the clinician responsible for the discharge in cases managed nonoperatively. Type of treatment was categorized according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures,<sup>16</sup> as either open appendectomy, laparoscopic appendectomy, conversion from laparoscopic to open appendectomy, abdominal/rectal drainage, or nonoperative treatment (see [–Supplementary Table S4](#), available in the online version). In the intension-to-treat analysis, laparoscopic appendectomy was grouped together with cases converted to open procedure. Independent variables and potential confounders were gender, age, and year of diagnosis.

### Statistical Analysis

Categorical variables were presented as frequencies and percentages, with univariate differences assessed by either chi-square test or Wilcoxon's rank-sum test. Continuous variables were generally nonnormally distributed, and reported as median with interquartile range (IQR). Time-dependent variables were presented with survival analysis using Kaplan–Meier's curves and 95% confidence intervals (CIs), with univariate differences assessed by log-rank test. Multivariable logistic regression and Cox's regression presented odds ratios (ORs) and hazard ratios (HRs) with 95% CIs, with adjustment for age in years, gender, year of diagnosis, type of clinical treatment, and type of appendicitis forced into the model. Age and year of diagnosis were ordered categorically, whereas type

**Table 1** Clinical management of children diagnosed with appendicitis in Sweden from 2001 to 2014

	Open surgery	Laparoscopy	Converted	Drainage	Nonsurgical	p-Value <sup>a</sup>
Total, n (%)	24,981 (64.2)	9,827 (25.2)	1,680 (4.3)	111 (0.3)	2,340 (6.0)	
Gender, n (%)						
Female	8,964 (35.9)	5,309 (54.0)	1,185 (70.5)	51 (45.9)	1,095 (46.8)	<0.001
Male	16,017 (64.1)	4,518 (46.0)	495 (29.5)	60 (54.1)	1,245 (53.2)	
Age, median (IQR)						
Age, y	12 (9–15)	14 (11–17)	15 (13–17)	13 (8–15)	13 (9–16)	
Disease severity, n (%)						
Uncomplicated	20,778 (83.2)	8,784 (89.4)	1,169 (69.6)	43 (38.7)	1,604 (68.5)	<0.001
Complicated	4,203 (16.8)	1,043 (10.6)	511 (30.4)	68 (61.3)	736 (31.5)	

Abbreviation: IQR, interquartile range.

<sup>a</sup>Chi-square test.

of treatment was the nominal category in the multivariable models. Sensitivity to unmeasured confounding in the multivariable models was quantified by *E*-values and 95% CI.<sup>17</sup> Stata/SE 14.1 for Windows was used for statistics.

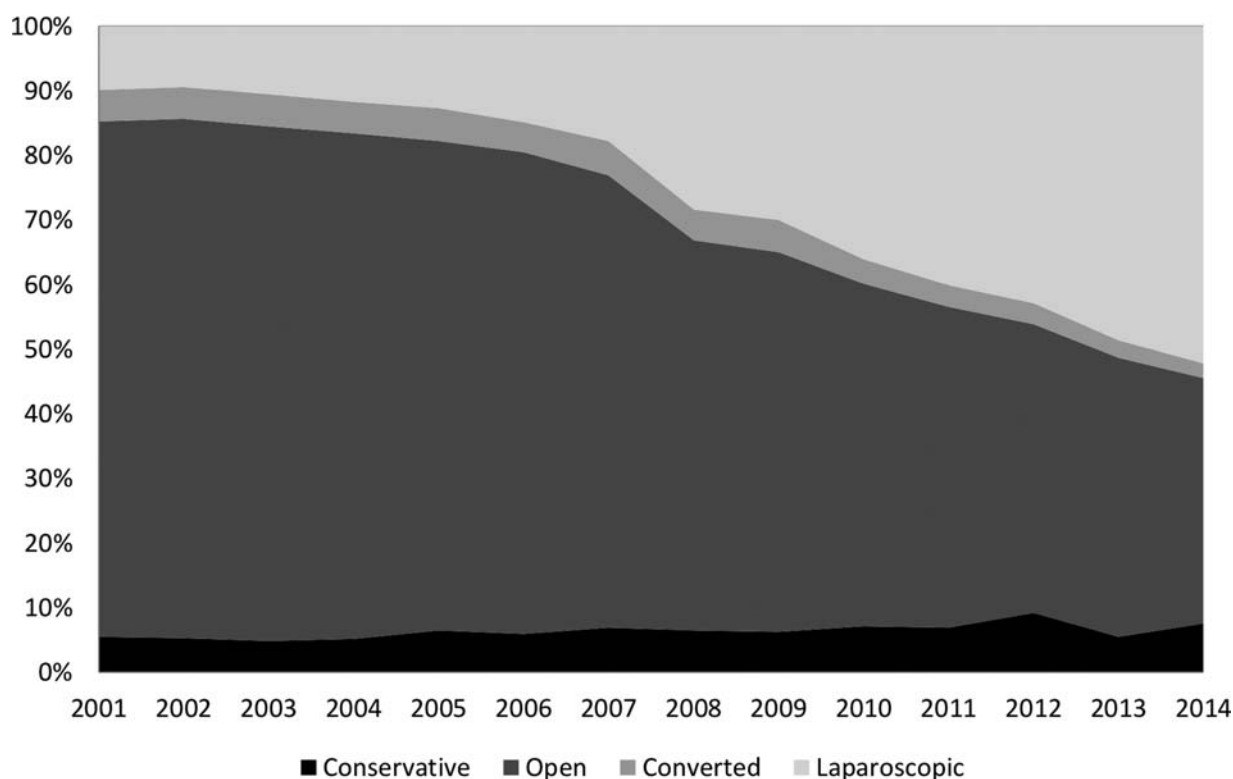
### Ethical Considerations

Unique personal identity numbers were available only to the register holder, and patient data were anonymized. As a result, no patients were directly identifiable, and informed consent was not possible to obtain. Ethical approval was granted by the Regional Ethical Review Board in Lund (DNR 2014/792) and the Central Ethical Review Board in Stockholm (DNR Ö 18-2015).

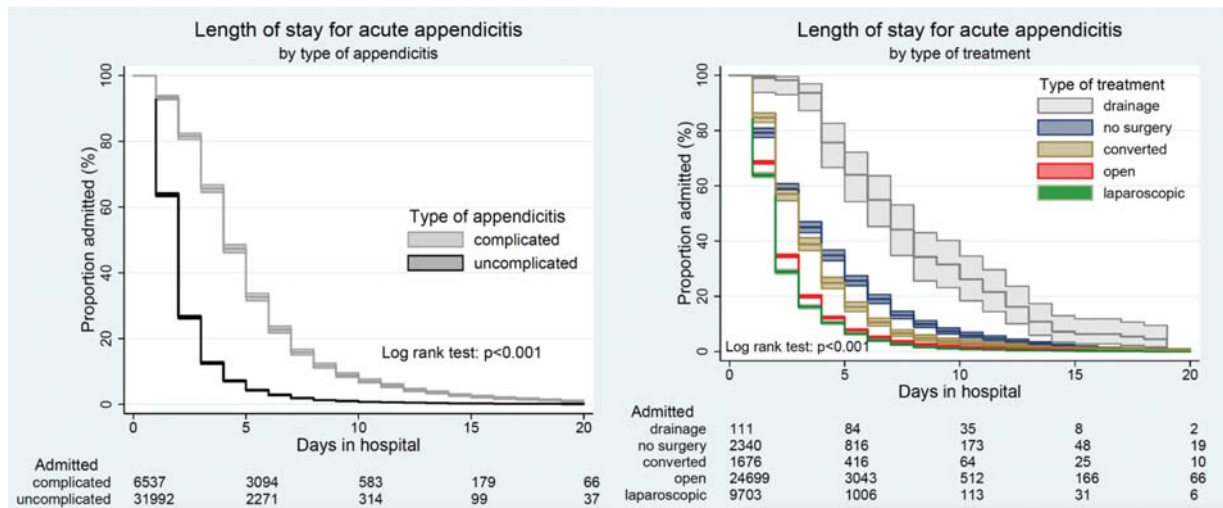
## Results

### Surgical Management of Appendicitis

Overall, 94.0% of Swedish children had surgery for their appendicitis (→Table 1). Girls were more likely than boys to be treated nonsurgically (adjusted OR [aOR]: 1.20 [95% CI: 1.10–1.30],  $p < 0.001$ ), and girls also had more laparoscopic surgery (aOR: 2.12 [95% CI: 2.02–2.23],  $p < 0.001$ ). Laparoscopic approach increased from 10.0% in 2001 to 52.2% in 2014, whereas conversions to open appendectomy decreased from 4.9 to 2.3% (→Fig. 1). Younger children were less likely to have laparoscopic appendectomy, with no clear association with



**Fig. 1** Treatment for pediatric appendicitis in Sweden 2001 to 2014. Laparoscopic treatment increased from 10 to 52%. Nonoperative management remained unchanged throughout the study period, and open appendectomies and laparoscopic appendectomies converted to open procedures were reduced by half.



**Fig. 2** Length of stay in hospital (with 95% confidence intervals) for appendicitis in Swedish children age 0 to 18 years, 2001 to 2014. (A) By appendicitis type (log-rank test:  $p < 0.001$ ). (B) By treatment modality (log-rank test:  $p < 0.001$ ).

conversion frequency; 16.8% of all appendectomies were intended laparoscopically among children <5 years of age and 2.7% were converted, as compared with children >14 years of age where 38.5% of appendectomies were intended laparoscopically and 6.9% were converted to open approach.

### Length of Stay

Median length of stay in hospital was 2 days (IQR: 1–3 days). Time in hospital doubled after complicated appendicitis compared with uncomplicated appendicitis (4 [IQR: 3–6] days vs. 2 [IQR: 1–3] days, Wilcoxon's rank-sum test,  $p < 0.001$ ) (–Fig. 2A). Length of stay was associated with age; children <5 years of age with uncomplicated appendicitis had a median length of stay of 3 days (IQR: 2–5 days), and 5 days (IQR: 4–7 days) following complicated appendicitis, compared with 2 days (IQR: 1–2 days) and 4 days (IQR: 2–5 days), respectively, among children >14 years of age. Length of stay was also associated with surgical management ( $p < 0.001$ ) (–Fig. 2B).

### Surgical Site Infection

Surgical site infections occurred in 2.8% (95% CI: 2.5–3.0%), without trends over time or age, and without gender differences (2.6% in girls vs. 2.9% in boys, aOR: 1.09 [95% CI: 0.92–1.29],  $p = 0.31$ ). Postoperative infection was more common after complicated appendicitis, compared with uncomplicated disease (5.9 vs. 2.3%, aOR: 2.64 [95% CI: 2.18–3.18],  $p < 0.001$ . *E-value*: 4.7 [95% CI: 3.8]). Fewer infections occurred after laparoscopic appendectomy compared with open appendectomy (2.0 vs. 3.1%, aOR: 0.65 [95% CI: 0.54–0.79],  $p < 0.001$ . *E-value*: 2.4 [95% CI: 1.8]), and increased significantly after conversion (5.0%, aOR: 1.41 [95% CI: 1.02–1.95],  $p = 0.04$ . *E-value*: 2.2 [95% CI: 1.2]) (–Table 2). In the intention-to-treat analysis, the risk for surgical site infection remained lower following intended laparoscopic approach than open appendectomy (2.3 vs. 3.1%, aOR: 0.74 [95% CI: 0.62–0.89],  $p = 0.001$ . *E-value*: 2.0 [95% CI: 1.5]).

### Readmission, Reoperation, and Mortality within 30 Days

Unplanned readmission within 30 days was required for 1.9% of the patients, and was more common following complicated appendicitis than uncomplicated appendicitis (5.5 vs. 1.2%, aOR: 4.75 [95% CI: 4.08–5.53],  $p < 0.001$ . *E-value*: 9.0 [95% CI: 7.6]) (–Supplementary Table S5, available in the online version), and after converted laparoscopic surgery as compared with open appendectomy (2.9 vs. 1.7%, aOR: 1.41 [95% CI: 1.04–1.93],  $p = 0.03$ . *E-value*: 2.2 [95% CI: 1.2]) (–Table 2). There was no difference in readmission rate following intended laparoscopic approach compared with open appendectomy (1.7 vs. 1.6%, aOR: 1.00 [95% CI: 0.82–1.21],  $p = 0.99$ ). Among 754 readmitted patients, 337 had additional abdominal surgery or drainage within 30 days (2.2% following complicated vs. 0.6% following uncomplicated appendicitis,  $p < 0.001$ ). For readmission, reoperation, and mortality within 30 days, there were no remaining gender differences after adjustment for differences in age, year, disease severity, and treatment modality, nor were there changes over time. All but two children in the cohort survived 30 days; one died following peritonitis at the age of 2 years and one due to multiple organ failure at the age of 8 years.

### Long-Term Risk of Surgery for Small Bowel Obstruction

Complicated appendicitis was associated with a higher risk for SBO during follow-up compared with uncomplicated appendicitis (0.7 vs. 0.2%, aHR: 3.89 [95% CI: 2.61–5.78],  $p < 0.001$ . *E-value*: 7.2 [95% CI: 4.7]) (–Fig. 3). Long-term risk of surgery for SBO was also associated with surgical management ( $p < 0.001$ ) (–Fig. 4A, B). Compared with open appendectomy, the risk of SBO was lower in children treated with laparoscopic appendectomy (cumulative incidence <0.1% following laparoscopic vs. 0.3% following open appendectomy, adjusted for gender, age, year of treatment, and appendicitis severity; HR: 0.27 [95% CI: 0.11–0.63],  $p = 0.002$ . *E-value*: 6.9 [95% CI: 2.6]), and this risk increased after converted procedures (cumulative incidence 1.0 vs. 0.3%, adjusted for gender, age, year of treatment, and

**Table 2** Surgical site infection and readmission after childhood appendicitis, by appendicitis type and operative modality

	No, n (%)	Yes, n (%)	aOR	OR (95% CI)	p-Value
Surgical site infection < 30 d					
Appendicitis type					
Uncomplicated	18,865 (97.7)	443 (2.3)		1	–
Complicated	2,698 (94.1)	168 (5.9)		2.64 (2.18–3.18)	<0.001
Operative modality					
Open	12,623 (96.9)	398 (3.1)	1	–	
Laparoscopic	8,026 (98.0)	163 (2.0)	0.65 (0.54–0.79)	<0.001	
Converted	882 (95.0)	46 (5.0)	1.41 (1.02–1.95)	0.04	
Drainage	60 (89.5)	7 (10.5)	2.80 (1.26–6.22)	0.01	
Readmission <30 d					
Appendicitis type					
Uncomplicated	31,924 (98.8%)	389 (1.2)		1	–
Complicated	6,261 (94.5%)	365 (5.5)		4.75 (4.08–5.53)	<0.001
Operative modality					
Open	24,562 (98.3%)	419 (1.7%)	1	–	
Laparoscopic	9,691 (98.6%)	136 (1.4%)	0.90 (0.73–1.11)	0.34	
Converted	1,631 (97.1%)	49 (2.9%)	1.41 (1.04–1.93)	0.03	
Drainage	102 (91.9%)	9 (8.1%)	2.70 (1.34–5.43)	0.005	
Nonsurgical	2,199 (94.0%)	141 (6.0%)	2.83 (2.31–3.47)	<0.001	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

Note: Odds ratio and 95% confidence intervals derived from multivariable logistic regression with age, gender, year, appendicitis type, and operative modality included in the model. Surgical site infection for years 2006 to 2014. Readmission for years 2001 to 2014.

appendicitis severity; HR: 2.93 [95% CI: 1.64–5.22],  $p < 0.001$ . *E*-value: 5.3 [95% CI: 2.7]). In the intention-to-treat analysis, the overall risk for SBO was similar for intended laparoscopic appendectomy compared with intended open appendectomy, both for complicated as well as uncomplicated appendicitis (→ Fig. 4C, D). These findings were stable in the multivariable analysis (complicated appendicitis: aHR: 0.78 [95% CI: 0.36–1.69],  $p = 0.53$ ; uncomplicated appendicitis: aHR: 0.85 [95% CI: 0.43–1.70],  $p = 0.65$ ).

## Discussion

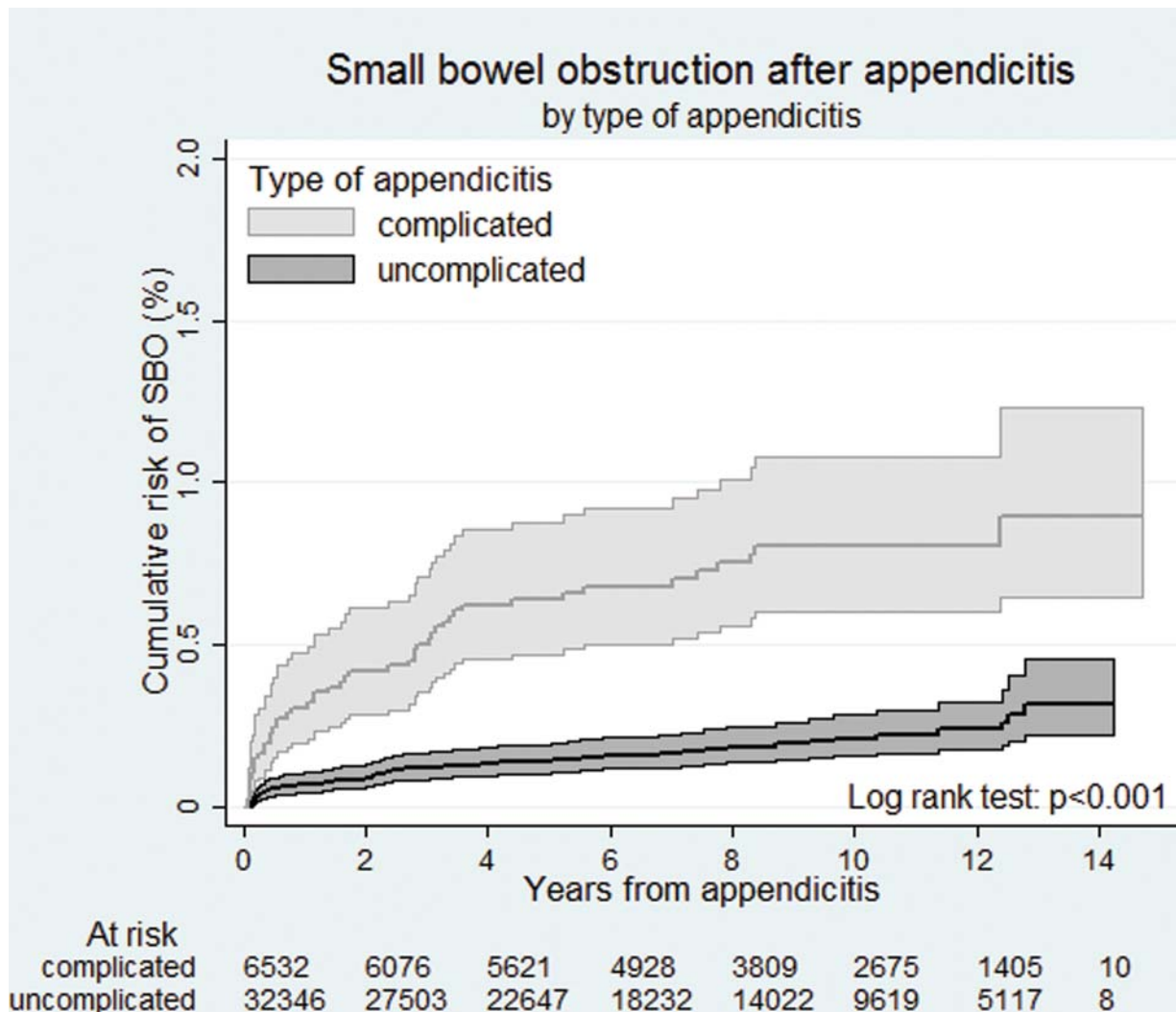
This national cohort study of pediatric appendicitis over a 14-year time period underlines the increase in morbidity following complicated appendicitis, with longer hospital stay, more postoperative infections, readmissions, reoperations, and higher long-term risk of SBO. Laparoscopic appendectomy was independently associated with fewer surgical site infections compared with open appendectomy, and was associated with lower risk of SBO during follow-up, unless conversion to open appendectomy was required.

Today, children with appendicitis generally have a favorable prognosis. Yet, surgery and perioperative care of children with appendicitis can be both challenging and expensive, and avoiding complications is of the highest priority.<sup>5,18–20</sup> In line with earlier studies,<sup>14,21</sup> our data report a very low mortality and a low overall risk of complications, and we

conclude that treatment in general was safe and effective in several aspects. However, since appendicitis is relatively common during childhood and adolescence, even low rates of complications lead to significant disease burden and costs beyond the index hospitalization. Our study stresses the substantial increase in short- and long-term morbidities following complicated appendicitis in children.

In line with previous cohort studies in the adult population, we also confirm that these children are exposed to an increased cumulative risk of SBO also several years after appendicitis, particularly after complicated appendicitis.<sup>10,11,18</sup> Previous single-center studies have reported somewhat higher risks for SBO than we do, possibly due to their inclusion of nonoperatively managed cases, whereas one large register-based study of uncomplicated appendicitis reports ~0.4% cumulative risk over 3.2 years mean follow-up after appendectomy.<sup>12,13,18</sup> We conclude that the risk of SBO requiring additional surgery is highest within the first few years after the appendicitis episode, but the risk persists also several years later. To what extent uncomplicated appendicitis adds to the baseline risk of SBO remains to be evaluated, as the background risk in the pediatric population is not known. Earlier studies have reported higher rates of surgical site infections after appendectomy than we do: up to 5% after uncomplicated appendicitis and up to 21% after complicated appendicitis, but those rates were recorded with active follow-up using telephone questionnaires and searches in





**Fig. 3** Cumulative risk of SBO requiring surgery after appendicitis in Swedish children age 0 to 18 years, by type of appendicitis: complicated (light) versus uncomplicated appendicitis (dark). SBO, small bowel obstruction.

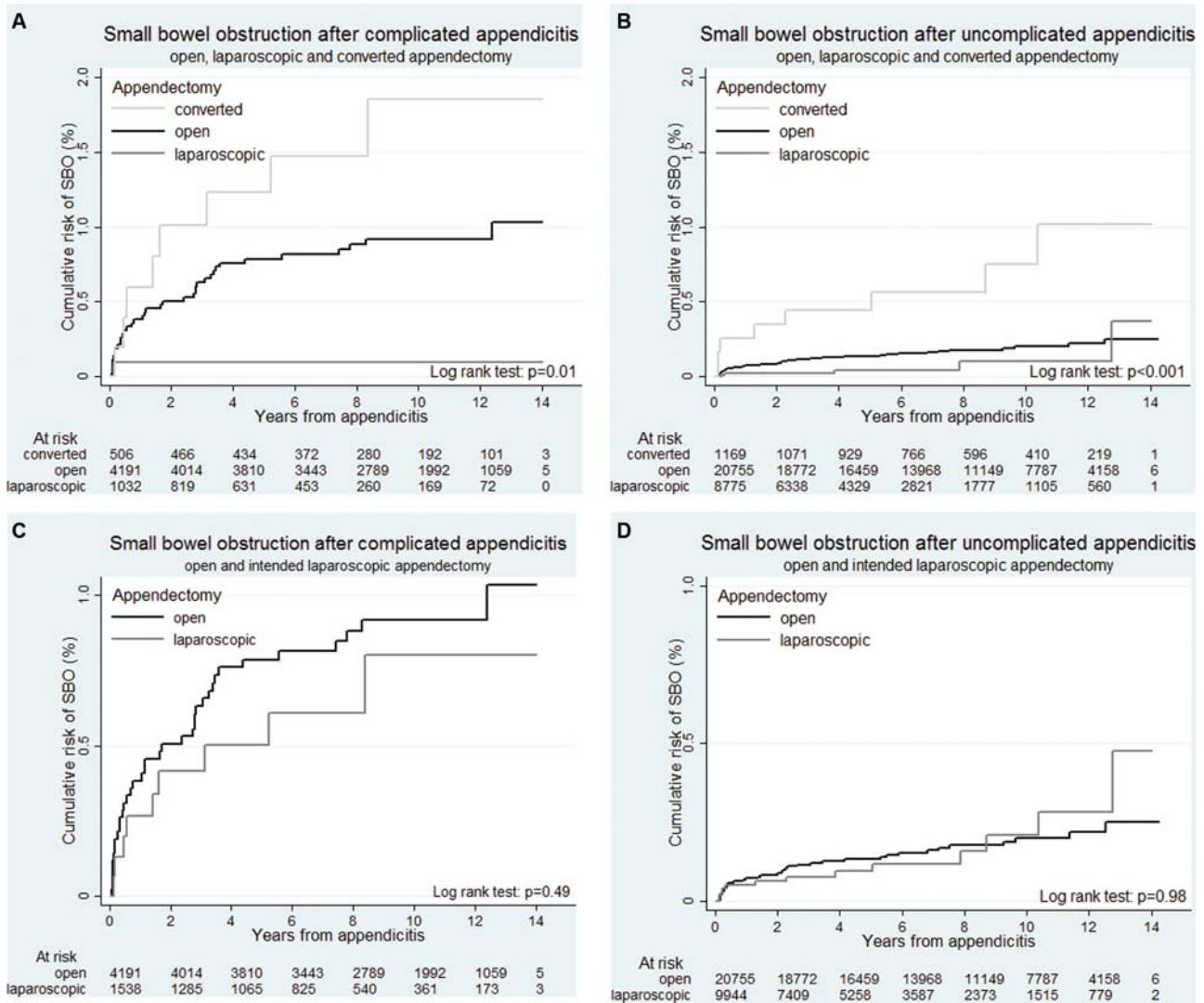
medical records.<sup>5,22-24</sup> However, the lower rates found in this study (2.3 and 5.9%, respectively) do not substantially differ from previous single-center reports.<sup>14</sup> It is important to bear in mind that comparisons between studies are sensitive to definitions of surgical site infection and by detection methods, as underreporting of milder cases of surgical site infections in health care registers is likely.<sup>25</sup>

The use of laparoscopic appendectomy increased markedly during the study period and has now reached more than 50% of pediatric appendicitis throughout Sweden. However, open appendectomy still accounts for a large proportion of appendectomies in children, and despite the predominance of laparoscopic approach in comparable health systems, surgeons in Sweden have been slow to adapt to this trend.<sup>26-29</sup> In an earlier retrospective single-center study conducted in a Swedish high-volume pediatric surgery institution, laparoscopic appendectomy did not differ from open appendectomy in terms of adverse events within 3 months.<sup>14</sup> Nonetheless, in our population-based study, laparoscopic appendectomy was associated with lower rates of surgical site infections, even when considering the increase in risk related to conversion to open proce-

dure. Further, laparoscopic appendectomy was also associated with lower risk of SBO in cases where conversion to open appendectomy could be avoided. Despite the lack of properly dimensioned randomized trials to assess the short- and long-term outcomes after pediatric appendicitis, efforts to implement laparoscopic appendectomy as a standard choice of treatment for children may also therefore improve overall morbidity and reduce costs.

#### Limitations

The Swedish National Inpatient Register has a diagnostic coverage rate of 99%, and high accuracy in reported diagnosis,<sup>15</sup> yet our findings must be interpreted within the context of the study design and data sources. In the revision of ICD-10 codes in 2010, the classification of the severity of appendicitis switched from an intraoperative determination, that is, perforation to a clinical one, that is, peritonitis. This shift was adjusted for in the multivariable analysis, and no substantial alterations were seen in the results in a sensitivity analysis prior and post the ICD-10 revision. As the risk of SBO in the background population was not known, this limited our



**Fig. 4** Cumulative risk of SBO requiring surgery after appendicitis in Swedish children age 0 to 18 years. The risk for SBO by surgical approach: laparoscopic appendectomy versus open and converted appendectomy in complicated (A) and uncomplicated appendicitis (B). Intended laparoscopic versus open appendectomy in complicated appendicitis (C) and uncomplicated appendicitis (D). SBO, small bowel obstruction.

interpretation of how uncomplicated appendicitis modified the long-term risk of SBO. Yet, we believe these findings to be valuable for clinicians in advising the child and family regarding the long-term consequences of appendicitis. We were not able to adjust for previous abdominal surgery, comorbidities, or risk factors for complicated appendicitis, such as occurrence of allergies.<sup>30</sup> Even if these factors may have influenced the choice of treatment modality, this is not expected to bias our results in a specific direction. Furthermore, although comparisons between treatment modalities were adjusted for disease severity, this may not capture gradients in the clinical risk. Selection bias and residual confounding must therefore be considered when interpreting our results; if more severe cases of appendicitis were selected for laparotomy rather than laparoscopic approach, this would have introduced confounding by indication, and it is also possible that follow-up was less likely after laparoscopic appendectomies than open procedures, and thus milder complications may not have been captured in the health care records to the same extent.

Misclassification related to intersurgeon variability may also introduce confounding that we are not able to adjust for in this study. Misclassification can be expected to dilute the estimated associations, if surgeons tend to aggravate rather than down-stage symptoms, so that even milder cases of peritonitis may be classified as generalized peritonitis. As determined by the *E*-value, however, given the strong measured association between intended laparoscopic versus open appendectomy and the risk of developing surgical site infection, an unmeasured confounder would need to be associated with the treatment modality and the risk of surgical site infection ~2.0-fold for the OR (and ~1.5-fold for the 95% CI) above and beyond the measured variables to explain the observed association between treatment modality and the risk of surgical site infection. Equally, an unmeasured confounder would need to be associated ~6.9-fold for the HR (2.6-fold for the 95% CI), above and beyond the measured variables, to explain the observed association between a nonconverted laparoscopic versus open appendectomy and the long-term risk of SBO.

## Conclusion

In this comprehensive national cohort study of childhood appendicitis, disease severity and laparoscopic surgery were evaluated for the risk of short- and long-term complications. The intention to perform a laparoscopic appendectomy was independently associated with fewer surgical site infections compared with open appendectomy, and successful laparoscopic appendectomy was also associated with lower risk of SBO during follow-up.

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### Conflict of Interest

None declared.

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