Long-term (19-26 years) outcome of non-operative treatment of appendicitis.

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Introduction

The longest outcomes reported of patients receiving non-operative treatment for acute appendicitis have been at five years[1].

Methods

Data were retrieved from the Swedish National Patient Registry on participants (n=292, 13 female and 279 male) in two randomized controlled trials (RCTs) of appendectomy vs. non-operative treatment for acute appendicitis (diagnosed clinically in 252 and with ultrasound in 40)[2,3] . Outcome extraction and analysis are described in the eMethods.

Results

These RCTs reported initial successful non-operative treatment in 95%[2]and 88%[3], and a one year recurrence rate of 36.8%[2] and 14.2%[3] in those that had been initially successfully managed non-operatively. 259/292 participants (88.7%) were traceable in the Register, 137/148 (92.6%) in the non-operative group and 122/144 (84.7%) in the appendectomy group (Figure 1A). In addition to the 21 (15%) participants who had appendectomy due to failure of non-operative treatment at initial hospital admission, 34 (29%) had a subsequent appendectomy for acute appendicitis, so that 82/137 (60%) patients had not undergone appendectomy at the end of follow-up (Figure 1B) and 82/116 (71%) who had been successfully discharged without appendectomy remained without appendectomy (Figure 1C). Though the rate of appendectomy was low after the first year, late appendectomies continued to occur even up to 20 years. In addition to those having appendectomy, 13 patients from the non-operative group went to a surgical outpatient clinic for abdominal pain, compared to 1 of the appendectomy group ($p<0.0015$). No patient from either group underwent surgery for bowel obstruction. Importantly, although appendiceal neoplasm can manifest as acute appendicitis, no appendiceal tumours were reported in the non-operative patients who underwent appendectomy during follow-up. Five patients had inflammatory bowel disease; three patients with Crohn's disease had all undergone appendectomy, (two randomised to appendectomy, one following

early failure of non-operative treatment), and two patients (one from each group) had ulcerative colitis.

Discussion

This study is the first to report truly long-terms results of non-operative treatment of acute appendicitis, by a registry study of patients included in two RCTs. The first was a pilot with 40 patients (13 female)[2] and the second was a multicentre RCT with 252 male patients[3]. The inclusion criteria were clinical evaluation and CRP level; ultrasound was only performed in the first study, which differs from current standards with routine imaging. Limitations of this study include: (i) this is a registry study and patients could not be followed prospectively; (ii) long-term outcomes were not part of the design of the original trials, which could result in outcome reporting bias; (iii) most patients in the trials were male; (iv) registry data were not specifically collected for the purpose of follow up of the RCTs (v) we do not have histopathology results after appendectomies in non-operative group and therefore, patients could have had acute uncomplicated appendicitis, perforated appendicitis, another (non-malignant) pathology or negative appendectomy; (vi) cost of treatment, including recurrence and time off work, could not be assessed in this study and should be considered as an important factors in the long term. In addition, we are looking at results of standards of diagnostics as they were when the initial studies were performed. This renders it difficult to extrapolate to current diagnostic standards, which involve much higher rates of imaging and consequently lower rates of both negative appendectomy and missed perforation.

However, more than half of the patients treated non-operatively did not experience recurrence and avoided surgery over approximately two decades. There is no evidence for long-term risks of non-operative management other than that of recurrence of appendicitis. The present data will further be beneficial to clinicians as well as patients with acute appendicitis in making a treatment decision.

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References

1. Salminen P, Tuominen R, Paajanen H, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. *JAMA*. Sep 25 2018;320(12):1259-1265. doi:10.1001/jama.2018.13201
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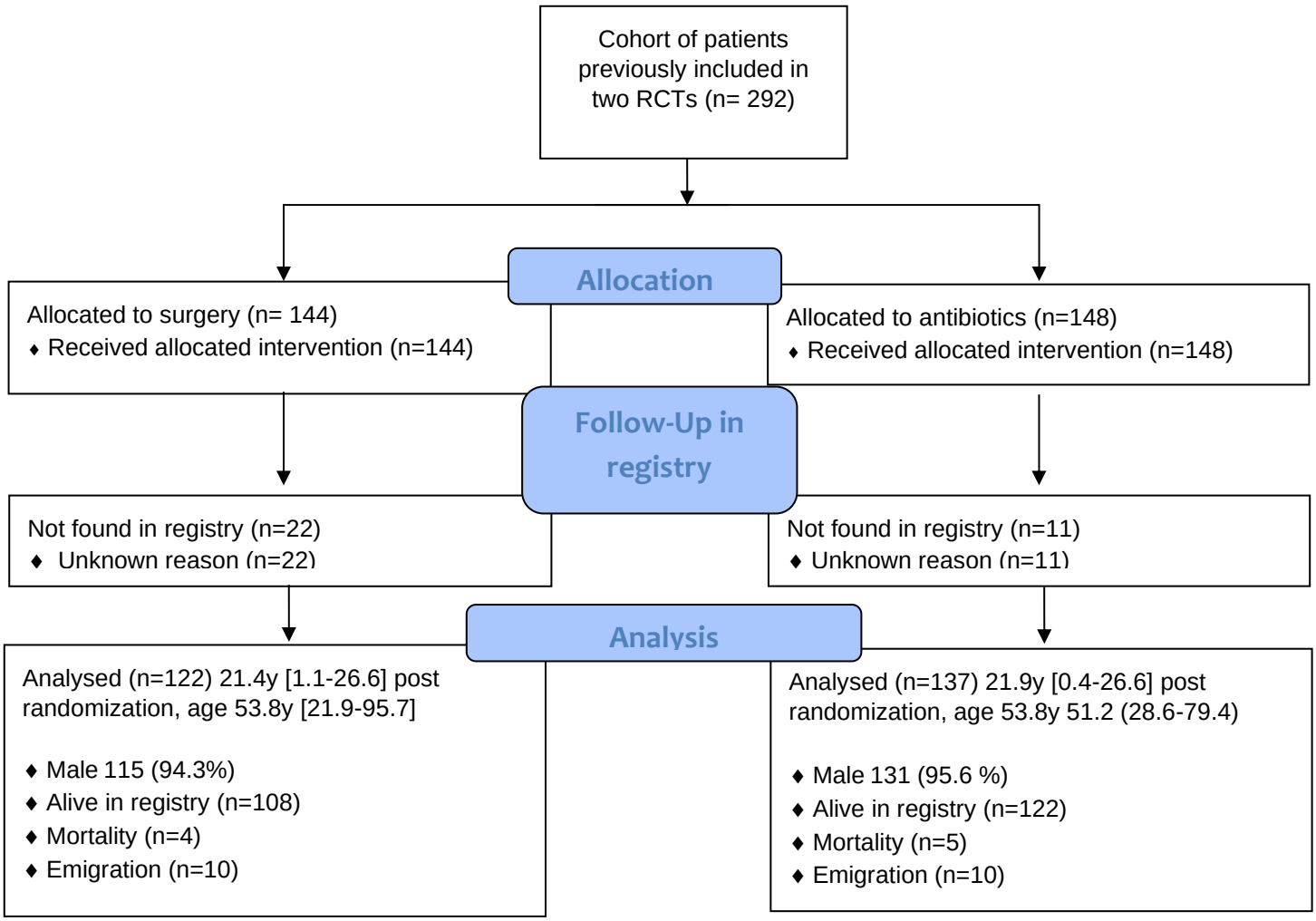
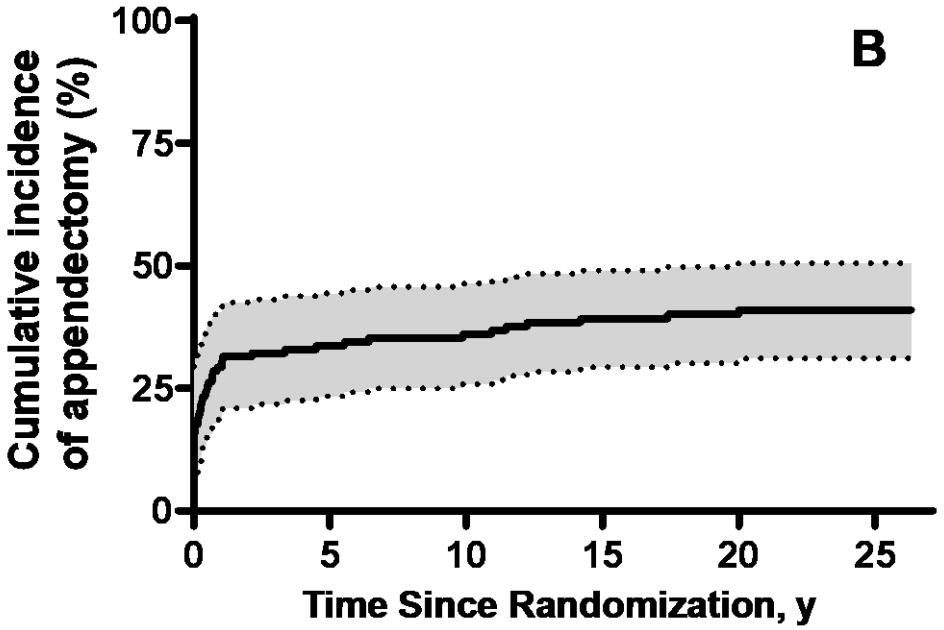
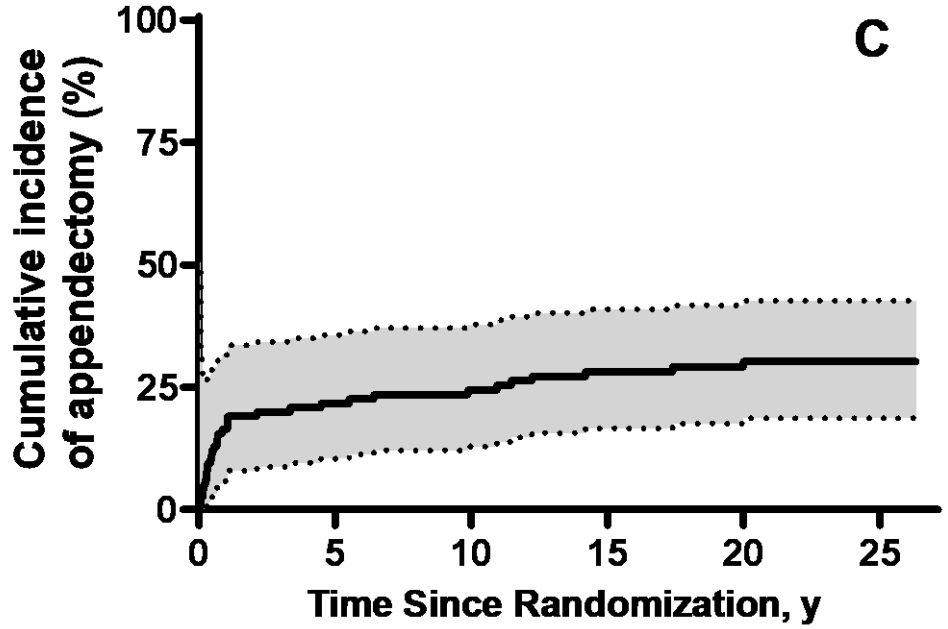
Figure 1 [A] CONSORT 2010 Diagram showing follow-up of the initial cohort**.** Cumulative incidence of appendectomy among patients in the non-operative treatment group up to 25 year follow up. [B] All patients randomised to non-operative treatment; [C] Patients who had been successfully treated non-operatively during their initial admission. Shaded area represents 95% Confidence Interval.





no. at risk	137	89	82	75	65	8



no. at risk	116	89	82	75	65	8

Supplementary Appendix

Supplement to: **Long-term (19-26 years) outcome of non-operative treatment of appendicitis**.

Methods

Study design/Data sources/measurement

This was a long-term (19 to 26-year) registry-based outcome of patients included in two prior randomised controlled trials concerning the non-operative treatment of acute appendicitis in adults, Eriksson[2] and Styrud[3]. In Sweden, since 1987, all patients admitted to hospitals in Sweden are registered in the Swedish Patient Register, by the National Board of Health and Welfare, which has collected patient, hospital, geographic, administrative and medical data. Since 2001 the register has also covered outpatient specialist care. The Swedish Cause of Death Register contains information on underlying causes of death since 1961. In addition, health care providers must report newly detected cancer cases to the population-based Swedish Cancer Register, which contains patient, medical and follow-up data. Statistics Sweden is responsible for official statistics and for other government statistics. They provide population statistics, and we used data from emigration population statistics from Sweden. We have queried the Swedish National Board of Health and Welfare of inpatient and outpatient register to identify patients who have been admitted to hospital and, or, treated in outpatient clinics in Sweden since the initial treatment for the acute non-perforated appendicitis. This cohort was checked against the Cancer Register and the Cause of Death Register to evaluate the other complications or the cause of death. We have also queried the Statistic Sweden for emigration from Sweden.

Settings

The Eriksson study (1995) was performed as a single centre randomised controlled trial in Stockholm. The Styrud study (2006) was a multi-centre study in six Swedish hospitals (Danderyd Hospital, St Göran Hospital Stockholm, Norrköping Hospital, Kristianstad Hospital, Borås Hospital, and Katrineholm Hospital). The study was registry-based and was performed at Karolinska Institutet in Stockholm. Data on the participants was collected from the registry, starting from initial admission and inclusion in the RCTs, and ending 31st of December 2018. Data were pseudonymised for the data collection and analysis.

Participants

All participants from both studies were eligible for inclusion. The Eriksson study included 40 patients aged 18-75 years (both women and men) who were randomised to surgery or antibiotic treatment between May 1992 and March 1994. The Styrud study included 252 men 18-50 years of age who were randomised to surgery or antibiotic treatment between March 1996 and June 1999. Diagnostic criteria were clinical suspicion of acute appendicitis and C-reactive protein > 10 mg/L, in the first study all patients underwent ultrasonography.

In total, 144 patients were randomised to appendectomy and 148 patients were randomised to antibiotic treatment. No patients were excluded so inclusion and exclusion criteria were as per the two original randomised controlled trials.

Variables

Admission for acute appendicitis was defined as ICD-9 and -10 codes 540A, 540X, K350, K351, K358, K359, in the inpatient and outpatient database[4]. Appendectomy was defined as procedure codes 4510, 4511, JEA00, JEA01, JEA10 according to the NOMESCO Classification of Surgical Procedures[5].

Follow up time was defined as time from randomization until 31st Dec 2018, unless patients had died or emigrated.

Statistics

Demographics were compared using Mann-Whitney test or by Fisher's exact test. A p value <0.05 was considered statistically significant.

References

1. Salminen P, Tuominen R, Paajanen H, et al. Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial. *JAMA*. Sep 25 2018;320(12):1259-1265. doi:10.1001/jama.2018.13201
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