Inflammatory Bowel Disease Is not Linked to a Higher Rate of Adverse Events in Colonoscopy—a Nationwide Population-based Study in Sweden

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1. Introduction

Colonoscopy is the current procedure of choice for the investigation of the lower gastrointestinal tract. It is generally a low-risk procedure, but adverse events occur. Population-based studies have shown incidence rates of post-colonoscopy bleeding across all indications to be between 0.05% and 1.1%, and incidence rates of post-colonoscopy perforations between 0.03% and 0.11%. A Swedish register study of colonoscopies between 2001 and 2013 reported an incidence of adverse events in colonoscopy. We evaluated whether inflammatory bowel disease and other potential risk factors are associated with bleeding or perforation in a nationwide, population-based, Swedish study.

Abstract

Background and Aims: Inflammatory bowel disease may cause long-standing inflammation and fibrosis and may increase the risk of adverse events in colonoscopy. We evaluated whether inflammatory bowel disease and other potential risk factors are associated with bleeding or perforation in a nationwide, population-based, Swedish study.

Methods: Data from 969,532 colonoscopies, including 164,012 (17%) on inflammatory bowel disease patients, between 2003 and 2019, were retrieved from the National Patient Registers. ICD-10 codes for bleeding [T810] and perforation [T812] within 30 days of the colonoscopy were recorded. Multivariable logistic regression was used to test if inflammatory bowel disease status, inpatient setting, time period, general anaesthesia, age, sex, endoscopic procedures, and antithrombotic treatment were associated with higher odds for bleeding and perforation.

Results: Bleeding and perforation were reported in 0.19% and 0.11% of all colonoscopies, respectively. Bleeding [odds ratio 0.66, p < 0.001] and perforation [odds ratio 0.79, p < 0.033] were less likely in colonoscopies in individuals with inflammatory bowel disease status. Bleeding and perforation were more common in inpatient than in outpatient inflammatory bowel disease colonoscopies. The odds for bleeding but not perforation increased between 2003 to 2019. General anaesthesia was associated with double the odds for perforation.

Conclusions: Individuals with inflammatory bowel disease did not have more adverse events compared with individuals without inflammatory bowel disease status. However, the inpatient setting was associated with more adverse events, particularly in inflammatory bowel disease status. General anaesthesia was associated with a greater risk of perforation.

Key Words: Gastrointestinal bleeding; perforation; inflammatory bowel disease
and perforation in Sweden from 2003 to 2019, and to determine if bleeding and perforation are more common in patients with IBD compared with patients without IBD, particularly in IBD patients with active disease. How the risk has changed over time, and the influence of risk factors including inpatient setting, general anaesthesia, procedures during colonoscopy and antithrombotic use, were also analysed.

2. Materials and Methods

2.1. Patients
This is nationwide, retrospective, cohort study of prospectively collected register data from the Swedish national patient registers and the Swedish prescribed drug register. These registers have previously been described. They cover almost 100% of the population and have been validated. By using personal identification numbers, data on each individual could be linked between the different registers. Information was collected on all individuals over 18 years of age, who had a colonoscopy between 2003 and 2019, by searching for the procedure codes for colonoscopy [UJF32 or UJF35]. The underlying population for this study was the entire adult population of Sweden in 2019 [about 8.3 million]. The study was approved by the Regional Ethics Review Board in Stockholm [Dnr 2015/690-31/2]. Informed consent was waived because of the retrospective nature of the study with the analysis using anonymised clinical data.

2.2. Outcome of adverse events
For this study we chose diagnostic codes that are specific for bleeding or perforation after a procedure [including colonoscopy], to avoid falsely capturing post-colonoscopy adverse events that had bleeding or perforation for other reasons. Bleeding or gastrointestinal haemorrhage was defined by the ICD-10 code T81.0 ‘Hemorrhage and hematoma complicating a procedure’ up to and including 30 days after the colonoscopy. Perforation was defined by the code T81.2 ‘Accidental puncture or laceration during a procedure’ up to and including 30 days after the colonoscopy.

2.3. Explanatory variables

2.3.1. IBD status
IBD diagnosis was defined using the ICD-10 codes for Crohn’s disease [CD] K50.X, ulcerative colitis [UC] K51.X, and indeterminate colitis [IC] K52.3. We searched the Swedish inpatient and outpatient registers from and including 1987 to 2019. Individuals were classified as having IBD if they had two diagnoses of IBD before or up to 6 months after the colonoscopy. For patients with a diagnosis of both CD and UC, the most recent diagnosis at the time of colonoscopy was used. Where an individual had received a diagnosis of IC plus CD or UC, they were defined as having CD or UC, respectively. Individuals consistently assigned a diagnosis of IC on two or more occasions were defined as having IC. Disease duration was calculated from the first entry into the patient registries which included an IBD diagnosis to the time of the colonoscopy. Disease duration is shown as a descriptive variable in Table 1.

2.3.2. Inpatient setting
Data on IBD disease activity were not available in the registered data. Performance of the colonoscopy in the inpatient [as opposed to outpatient] setting was used as a proxy for severe disease flare.

2.3.3. Time period

2.3.4. General anaesthesia
No data were available regarding which drugs were used for general anaesthesia; therefore, any general anaesthesia was compared with no anaesthesia. However, most endoscopy units in Sweden use propofol as an anaesthetic which has a short recovery time, and the individual can be discharged later the same day.

2.3.5. Demographics
Age was categorised into four groups, from 0–30, 31–50, 51–70 and 71+. The youngest age group was set as the reference. For sex, men were set as the reference. The number of

| Table 1. Patient and procedure characteristics per colonoscopy, in total, and according to presence/absence of IBD and as well as separated on IBD subtypes. |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Total                              | Non-IBD         | IBD             | UC              | CD              | IC              |
| n (%)                              | N = 969 532    | N = 805 520     | N = 164 012     | N = 96 849      | N = 64 027      | N = 3136        |
| General anaesthesia, n [%]         | 17,969 [1.9]   | 12,257 [1.5]   | 5,712 [3.5]    | 2,286 [2.4%]   | 3,283 [5.1%]   | 143 [4.6%]     |
| Dilatation, n [%]                  | 3,467 [0.4]    | 450 [0.1]      | 3,017 [1.8]    | 57 [0.1%]      | 2,953 [4.6%]   | 7 [0.2%]       |

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IC, indeterminate colitis; SE, standard error; NA, not available.

*Per individual 2003–2019.*
colonoscopies per individual over 2003–2019 is shown as a descriptive variable in Table 1.

2.3.6. Procedures during colonoscopy
This included polypectomy, dilatation [JFA58], and biopsy [UJF35]. Polypectomy includes simple polypectomy [JFA15] and endoscopy mucosal resection [JFA85]. Information on the number or size of polyps is not included in the registers.

2.3.7. Antithrombotic use
For antithrombotic medicine, the use of acetylsalicylic acid, other antiplatelet drugs, warfarin, and direct oral anticoagulants [DOACs], prescribed within the 3 months prior to the colonoscopy and registered in the Swedish Prescribed Drug Register, was used. Data regarding temporary stop of antithrombotic medicine in relation to the colonoscopies are not included in the register. However, most endoscopy units pause antithrombotic medicine before and during the colonoscopy, following recommendations from the Swedish Gastroenterology Society which are harmonised with the ESGE guidelines.

2.4. Statistical analysis
Patient and procedure characteristics per colonoscopy are presented in Table 1. Bivariate logistic regression was used to compare the odds of bleeding and perforation between individuals with IBD and individuals without IBD and for the other risk factors, respectively. The multivariable analyses included bleeding and perforation, respectively, as outcome variables, and the following exposure variables: IBD status, setting, time period, general anaesthesia, sex, age, procedure during colonoscopy [polypectomy, dilatation and biopsy], and the use of anticoagulants. In addition, we performed moderation analyses to test if the odds of adverse events in patients with and without IBD differed between inpatient and outpatient settings. In the moderation analyses, an interaction between IBD status and setting was added to the multivariable analyses. The analyses were clustered on patient identity, as some patients underwent several endoscopies during the study period. Also, in Supplementary Table 1 we present crude rates as percentages to simplify interpretation and application to clinical practice. A p-value <0.05 was considered statistically significant. All analyses were performed using Stata 17 [StataCorp, College Station, TX].

3. Results
During the period 2003–2019, 969,532 colonoscopies were performed in 661,080 adult individuals. Of these, 164,012 colonoscopies were performed on individuals with an IBD diagnosis, of which 59% were performed in patients with UC, 39% in patients with CD, and 2% in patients with IC, see Table 1. The mean disease duration in patients with IBD was 8.9 years, and IBD patients underwent significantly more colonoscopies compared with patients without IBD [Table 1]. For further patient and procedure characteristics on the study population, see Table 1.

3.1. Bleeding
The bleeding rate for all colonoscopies was 0.19%. The odds of bleeding were significantly lower in individuals with IBD compared with individuals without IBD (crude odds ratio [OR] = 0.42, 95% confidence interval [CI]: 0.34–0.50, p < 0.001, adjusted OR [AdjOR] = 0.66, p < 0.001). The odds of bleeding were significantly lower in UC compared with individuals without IBD [AdjOR = 0.62, p = 0.001], and CD compared with individuals without IBD [AdjOR = 0.69, p = 0.013]. The odds of bleeding were significantly higher in men, and increased with polypectomy, increasing age, and with antithrombotic use. Anaesthesia, dilatation, and biopsy were not associated with bleeding; see Table 2 for adjusted ORs. Crude ORs are presented in Supplementary Table 1.

3.1.1. Outpatient vs inpatient setting
The odds of bleeding were higher for colonoscopies performed in inpatient settings compared with outpatient settings [AdjOR = 4.87, p < 0.001], Table 2. Setting moderated the association between IBD status and bleeding, so that patients with IBD had increased odds for bleeding in inpatient setting compared with patients without IBD [OR for interaction between setting and IBD status = 1.44, p = 0.031].

3.1.2. Time period
The use of antithrombotic medicine and frequency of polypectomy increased from 2003–2007 to 2016–2019 [adjOR = 0.85, 95% CI: 0.47–0.70, p < 0.001, adjOR = 0.57, 95% CI: 0.47–0.70, p < 0.001, adjOR = 0.79, p = 0.033]. The odds of perforation were significantly lower in UC compared with individuals without IBD [adjOR = 0.61, p = 0.005], whereas no difference was found between CD and individuals without IBD [adjOR = 1.05, p = 0.752]. The odds of perforation were significantly higher in women and with polypectomy, dilatation, increasing age, and general anaesthesia, whereas antithrombotic use and biopsy were not associated with perforation risk. See Table 2 for adjusted ORs; crude ORs and crude rate are presented in Supplementary Table 1.

3.2. Perforation
The perforation rate for all colonoscopies was 0.11%. The odds of perforation were significantly lower in IBD patients compared with individuals without IBD [crude OR = 0.57, 95% CI: 0.47–0.70, p < 0.001, adjOR = 0.79, p = 0.033]. The odds of perforation were significantly lower in UC compared with individuals without IBD [adjOR = 0.61, p = 0.005], whereas no difference was found between CD and individuals without IBD [adjOR = 1.05, p = 0.752]. The odds of perforation were significantly higher in women and with polypectomy, dilatation, increasing age, and general anaesthesia, whereas antithrombotic use and biopsy were not associated with perforation risk. See Table 2 for adjusted ORs; crude ORs and crude rate are presented in Supplementary Table 1.

3.2.1. Outpatient vs inpatient setting
The odds of perforation were higher for colonoscopies performed in inpatient settings compared with outpatient settings [adjOR = 4.37, p < 0.001; Table 2]. Setting did not moderate the association between IBD status and perforation [OR for interaction 1.13, p = 0.568].

3.2.2. Time period
There was no change in adjusted odds for perforation over time from 2003–2007 to 2016–2019 [adjOR = 0.85, p = 0.093]; see also Table 3.

4. Discussion
In this nationwide register study, IBD status was not associated with a higher rate of adverse events after colonoscopy. However, setting, time period, and procedures were associated with increased bleeding and perforation in colonoscopy. Inpatient IBD colonoscopies had higher odds of bleeding compared with colonoscopies in IBD patients in the outpatient setting. General anaesthesia was associated with a 2-fold
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...increase in the odds of perforation. Women had lower odds of bleeding, but higher odds of perforation compared with men. Older age and polypectomy were associated with more frequent bleeding and perforation. The use of antithrombotic medicine was associated with higher odds of bleeding but not perforation. Dilatation was associated with increased odds of perforation but not bleeding.

The lower odds for bleeding and perforation in patients with IBD could be interpreted as indicating that IBD is protective against complications associated with colonoscopy. However, the lower risk may be due to residual confounding by indication. There is a qualitative difference in patients who undergo colonoscopy due to IBD compared with other indications such as bleeding or CRC surveillance. Non-IBD individuals are older, more often need polypectomy, and are more frequently treated with antithrombotic medicine. Although adjustment for these covariates was performed, it is likely that residual confounding variables that affect the outcome still exist. Overall, these data would suggest that IBD is not associated with higher risk of bleeding or perforation after a single colonoscopy. However, over the study period, individuals with an IBD diagnosis underwent twice as many colonoscopies as individuals without IBD, increasing their cumulative lifetime risk of adverse events.

Previous studies have reported conflicting results regarding the likelihood of adverse events in IBD colonoscopies, and there is a lack of population-based studies. In a large cohort study including 612 190 colonoscopies [33 732 IBD colonoscopies] Navaneethan et al. found an increased risk of perforation during colonoscopy in IBD patients compared with non-IBD controls, whereas Ferreira et al. in a single-centre study found that the risk of adverse events after each...
endoscopy in IBD patients was comparable to the risk in the general population, although patients with IBD had an elevated lifetime risk of adverse events after colonoscopies.\textsuperscript{13} In a case-control study, Mukewar 	extit{et al.} reported a significantly higher rate of perforation in IBD patients compared with non-IBD patients [18.91 per 10 000 and 2.50 per 10 000 procedures, respectively, \( p = 0.001 \)].\textsuperscript{12} Buisson 	extit{et al.} found no difference in perforation rate between IBD patients and controls in a large single-centre retrospective cohort study. However, of 16 patients with perforation in the control group, most had other risk factors for perforation, such as colon cancer, dilatation procedures, or polypectomy.\textsuperscript{14}

IBD disease activity is a factor that may be hypothesised to affect risk of complications after colonoscopy. Unfortunately, disease activity is not captured in the available data. Instead, colonoscopy performed in the inpatient setting was used as a proxy for active disease. In IBD patients undergoing colonoscopy in the inpatient setting compared with the outpatient setting, the odds of bleeding were almost seven times higher and the odds of perforation were almost five times higher. There are clear limitations to the extent to which inpatient status reflects IBD disease activity, and patients in this category may have been inpatients for other reasons, such as requirement for inpatient bowel cleansing or other conditions requiring inpatient care. Future studies linking endoscopic scores, histology, and colonoscopy outcomes might be able to address this question.

General anaesthesia was associated with a 2-fold increased likelihood of perforation. It may be hypothesised that this is due to the absence of feedback or pain signalling from the patient. Moreover, the lack of positional change might increase technical difficulty of the colonoscopy. Another possible explanation for the increase in adverse events associated with general anaesthesia is due to confounding by indication. For example, a stricture in the colon might cause more pain during colonoscopy and therefore prompt general anaesthesia, but the same stricture might also increase the likelihood of perforation. This finding of higher odds of perforation when general anaesthesia is employed is in keeping with previous reports. Both Cooper in the USA\textsuperscript{19} and in Adeyemo 	extit{et al.} in Spain\textsuperscript{20} demonstrated an increased risk of perforation during general anaesthesia. However, Bielawska 	extit{et al.} found no increase in perforation risk.\textsuperscript{21}

The odds of bleeding increased from 2003–2007 to 2016–2019. Some of the increase may be explained by an increase in antithrombotic use as well as an increase in polypectomy frequency [Table 3]. During the study period, development in techniques/methods that replace surgery, such as endoscopy mucosal resection and endoscopic submucosal dissection, have made it possible to remove endoscopically larger polyps, which might also contribute to this increase.\textsuperscript{22,23} However, there was no increase in the odds of perforation over the 17-year study period, which might be considered counterintuitive when considering the increase in the removal of large polyps over the same period. On the other hand, these results might also reflect the increased training and skill among therapeutic endoscopists.

Other results of this study are mostly in line with previous studies, including the findings that polypectomy is associated with increased likelihood of bleeding and perforation.\textsuperscript{24} that the rates of bleeding and perforation increase with age,\textsuperscript{1,24} that antithrombotic medicine is associated with an increased risk of bleeding,\textsuperscript{25,26} and that dilatation is associated with an increased risk of perforation.\textsuperscript{27}

The strength of this study is the nationwide, population-based design including almost one million colonoscopies. The population-based nature makes it less prone to selection bias compared with studies that employ patient selection, for example including patients entering a colorectal cancer screening programme or patients treated at tertiary referral centre.

The main limitation of this study, in common with other register-based studies, is that the analyses are limited to the data available in the registers. In the current study, we did not have information on disease activity and instead had to use a proxy for that in the form of inpatient setting. Other data that are not available and could affect the outcome are: if and at what time antithrombotic medicine was discontinued; if another antithrombotic medicine temporarily replaced it; the completion rate of the colonoscopies; and bowel preparation. Another possible source of bias is in the case of an individual who has an adverse event in an outpatient setting and then gets admitted to a hospital; this would be registered as an inpatient colonoscopy. Finally, our definition of a bleeding or perforation, by using the codes T81.0 and T81.2 up to 30 days after a colonoscopy, might capture gastrointestinal [GI] bleeding caused by procedures other than colonoscopy. But we think this is rare, and it does not systematically affect one group more than another. As such, it should not skew the overall message of these data.

In conclusion, bleeding and perforation were rare and were not more common in colonoscopies in individuals with IBD compared with those without IBD. However, IBD inpatients had marked increased odds for adverse events, suggesting that disease activity may be a significant risk factor and that extra care is warranted in patients with IBD when they undergo colonoscopy as an inpatient. Several common procedures during colonoscopy increased the risk of adverse events in general. Notably, general anaesthesia during colonoscopy was associated with a greater risk of perforation.

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**Conflict of Interest**

All authors declare no conflict of interest.

**Author Contributions**

BA: drafting manuscript, statistical analysis, review of manuscript. AA: statistical analysis, review of manuscript. CH: review of manuscript. GB: review of manuscript. PTS: study design, review of manuscript, obtaining funding. AF: study design, acquisition of data, review of manuscript, obtaining funding. A part of the data was previously published as a poster on the UEGW 2022 in Vienna.
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Data Availability
The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request, including an ethical permission that is approved, to the corresponding author.

Supplementary Data
Supplementary data are available at ECCO-JCC online.

References
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** Data from a post-hoc analysis of diary data from the double-blind, randomised, placebo-controlled 58-week SELECTION trial. Achievement of stool frequency subscore of ≤1 by Day 3 in biologic-naïve patients, and rectal bleeding subscore of 0 by Day 5 in biologic-experienced patients.‡
† Interim analysis of SELECTIONLTE assessing the efficacy and safety of open-label JYSELECA 200 mg through LTE Week 144 in completers and LTE Week 192 in non-responders, respectively, representing a total of 3.9 years of treatment each (completers: 58 + 144 weeks; non-responders 10 + 192 weeks).§
†† Determined in a post-hoc exploratory analysis of the SELECTION trial assessing HRQoL and the comprehensive disease control multi-component endpoint, which comprises both clinical and QoL outcomes, in individuals receiving JYSELECA (n=786).∥ Each patient has their own definition of normal life.

This medicine is subject to additional monitoring.

HRQoL, Health-related quality of life; LTE, Long term extension; QoL, Quality of life; UC, Ulcerative colitis.

1. JYSELECA Summary of Product Characteristics, January 2024.