The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12 230 patients

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TITLE PAGE

Title

The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12,230 patients

Short Title

Surgery risk following right hemicolectomy for Crohn's Disease

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Summary

Background

Crohn's Disease (CD) has a high-risk of bowel resection and later surgery for recurrent disease. Recent guidelines advocate colonoscopy 6-12 months following surgery to reduce further surgical intervention through medical therapy intensification.

Aims

To investigate the risk of further surgery at the anastomosis following right hemicolectomy for CD.

Methods

Hospital Episode Statistics were used to identify patients with CD and a right hemicolectomy between 2007-2016. Adherence to post-resection colonoscopy guidance timing and risk of further surgery at the anastomosis were examined. Cox proportional hazards models assessed risk factors for further surgery.

Results

12,230 patients were identified: 45% male; median age 36 (IQR 26-49) years. Median follow-up was 5.9 (IQR3.6-8.6) years: totalling 74,960 person-years. Median time to further surgery was 2.9 (IQR1.2-5.3) years. By 5-years 9%, and 10-years 16.9% of those with sufficient follow-up had at least one further surgery at the anastomotic site. Older, less deprived patients, and those whose index surgery took place on an elective admission were associated with reduced further surgery risk. The annual number of right hemicolectomies increased over the study from 1,063 to 1,317, driven by increasing prevalence of CD. Overall, 78% of patients did not have a colonoscopy, as recommended, within 6-12 months following index resection.

Conclusions

Further surgery at the anastomotic site remains common following index right hemicolectomy for CD. Post-surgical colonoscopy was only undertaken in 22% of patients within suggested timeframes. Increased

colonoscopy may lead to a reduced need for surgery if early optimisation of medical therapy is undertaken for recurrence.

Key Words

Inflammatory Bowel Disease, Crohn's Disease, Colectomy, Colonoscopy.

Author contributions

Study concept and design was jointly conceived by DK, BC, AD, PP and NT. Data extraction was performed by BC and AD and analysis was performed by BC and DK. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors.

Abbreviations

Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), Hospital Episode Statistics (HES), Odds Ratio (OR), interquartile range (IQR).

Introduction

Crohn's Disease (CD) is a relapsing and remitting disease of the gastrointestinal tract. Principally localising to the small and/or large bowel, it leads to transmural inflammation, stricturing and fistulisation [1]. The condition can be debilitating, leading to time in hospital, restricting employability and reducing quality of life [2]. Surgical resection is indicated for patients who have struggled with symptoms despite medical management or when fibrosis is established. Although there has been a fall in rates of surgery for CD over time, rates remain high with up to 50% of patients undergoing resection within 10 years of a CD diagnosis and lifetime risks exceeding 70% [3–5]. Recurrent symptomatic disease following surgery is common with further surgery at 5 and 10 years reported to be 24 and 35% respectively [6,7]. Most commonly seen following ileocaecal resection, recurrent CD at the anastomosis is often severe in terms of mucosal inflammation (Rutgeerts score >i2) but is less often symptomatic [8–10]. However, given that a recommended therapeutic goal in inflammatory bowel disease (IBD) is to achieve mucosal healing to prevent further complications of stricturing and penetrating disease, it is recommended that efforts are made to mitigate the risk of recurrence through proactive investigation and treatment escalation. The recommendation to undertake ileocolonoscopy following resectional surgery such as right hemi colectomy is now established in national and international guidelines [4,11,12]. Improved endoscopic and clinical recurrence rates were reported in CD surgical patients who underwent early colonoscopy and had an escalation in their treatment for recurrent CD [8,9,13,14].

The aim of this study was to investigate the risk of further surgery following a right hemicolectomy for CD in England and the adherence to post-operative ileocolonoscopy as recommended in guidelines.

Methods and materials

Data source

Hospital Episode Statistics (HES) is a database including information on all episodes of National Health Service (NHS) secondary care treatment within England. HES contains diagnostic (International Classification of Diseases version 10 (ICD10)) and procedural (Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision (OPCS-4)) information. Demographic and geographic data for each patient are also recorded. Individuals can be tracked through their hospital admissions via a unique identifier. Mortality data is obtained by linking to the Office for National Statistics (ONS) database. The HES data sharing agreement prohibits the publication of potentially identifiable data and it is for this reason that patient counts of five or less are suppressed from publication.

Inclusion criteria

Adult patients over 18 years old were identified for inclusion in the study by extraction of all instances of right hemicolectomy/ileocaecectomy codes (H06 and H07) in HES and then identifying all patients who had their first (index) occurrence of one of these surgical procedures between 1st January 2007 and 31st December 2016. Note that the code encompassing ileocaecectomy is included within the right hemicolectomy code and therefore right hemicolectomy will be used hereafter to include ileocaecectomy. For inclusion, a patient was required to have a Crohn's disease (ICD-10: K50) diagnosis at the time of their index surgery admission.

Exclusion criteria

Patients were excluded from the study if they had an ulcerative colitis (UC) (ICD-10: K51) diagnosis coded subsequently, suggesting a misclassification of CD. Patients were further excluded if they had a cancer diagnosis during the year before index surgery or during the follow-up period. Patients without a recorded age, those under the age of 18 at the time of index surgery and those with missing or invalid sex data were also excluded, as were patients not resident in England. Further resectional surgery that took place either during the same spell or within a 30-day period following index surgery were excluded from the analysis. Patients with index surgical codes resulting in a stoma and therefore at risk of requiring a subsequent elective staged procedure not causally related to Crohn's disease were examined (Appendix 1). Further operations undertaken during an elective admission and within one year of such index surgery were excluded from analysis in order to limit bias associated with the planned completion of the initial intent of the index surgery but the patients themselves were not excluded from the analysis of later further resectional surgery at the anastomosis site.

Data validation

To assess the validity of CD surgical coding, a list of patients meeting the same ICD-10 and OPCS-4 coding criteria was provided by the local coding departments at Sandwell and West Birmingham Hospitals NHS Trust. The accuracy of coding was then assessed by consulting the electronic patient records to establish if the CD diagnosis and the surgical procedural code were reliable. Colonoscopy undertaken within 6-12 months following right hemicolectomy (as recorded in the patient's notes) was compared to HES data recorded for the hospital.

Demographic data

Patient age, sex, region of residence, deprivation status and ethnicity were identified from index surgery admission coding. Age was divided into quintiles at 18-24, 25-31, 32-41, 42-53 and ≥54. Ethnicity was stratified into White, Asian, other minority ethnicities and unknown. The Charlson comorbidity index, a measure of multimorbidity in patients and previously validated in HES [15], was calculated using secondary diagnostic coding. Deprivation quintiles were calculated from the Index of Multiple Deprivations, a classification based on income, employment, crime and living environment [16]. Deprivation quintile 5 is the least deprived quintile, while quintile 1 is the most deprived.

Outcome measures

The primary outcome measure in this study was further resectional surgery at the site of index right hemicolectomy surgery. The time interval between index and first further surgery for recurrent CD was examined along with the mechanism of admission (elective or emergency). The end of the follow-up period for further surgery was 31st December 2018, providing a minimum of two and a maximum of twelve years' follow-up. The annual point prevalence of CD in England, derived from a previous primary care study, was used to examine the trends in index right hemicolectomy over the study period [17].

A secondary outcome measure examined in this study was the number of patients who underwent colonoscopic procedures following index right hemicolectomy. Colonoscopy (ileocaecoscopy) undertaken 6-12 months following index surgery was considered valid. Patients without a colonoscopy within this 6-12 month time period were examined for reasonable obstacles, including further surgery within the time period (staged elective or emergency), death, a relevant illness or procedure that might prevent or delay colonoscopy (Appendix 2). Colonoscopy performed at any time from index surgery to 24 months following surgery was also recorded. Imaging modalities with the potential to screen for recurrent disease post-surgery, including MRI, CT, barium or capsule endoscopy were further examined. To demonstrate national trends over the study period, numbers of colonoscopies performed in England and those performed on patients with a CD diagnosis were also examined.

Statistical analysis

Demographic tables were produced showing figures for first surgery, further surgery at one year and all subsequent surgeries during follow-up. Age and time to follow-up surgery is presented as median and interquartile range (IQR). Index right hemicolectomy counts for CD in England were divided by number of CD patients in England per year of the study and presented as rate per 1000 patients with CD. The number of adults with CD in England per year of the study period was derived from Office for National Statistics (ONS) population data for England and estimates of CD prevalence in England derived from a nationally representative primary care database [17,18]. A linear regression model was fitted to the trend of yearly right hemicolectomy rates over the study period to assess change. Index surgeries were subdivided into those that took place on an elective admission and those that took place on an emergency admission.

A Cox proportional hazards model was produced for time to further surgery with results presented as adjusted hazard ratios (aHR), and a Kaplan-Meier curve of failures defined as further surgery based on index admission method was produced. A further Kaplan-Meier plot with three survival curves representing three periods of index surgery was produced with accompanying global and stratified log rank tests. Proportional hazards assumptions were tested and satisfied. Variables included in the Cox regression model were age, sex, provider volume of right hemicolectomy for CD, ethnicity, deprivation, index surgery admission method, Charlson comorbidity score, year of index right hemicolectomy, prior perianal disease and laparoscopic index surgery. Perianal surgery was used as a surrogate for severe perianal surgery. Characteristics of included and excluded patients were compared using Chi-squared tests for categorical data. Demographic data is presented as counts and percentage where applicable.

A sensitivity analysis (Cox proportional hazards model) was undertaken to account for all first further surgery following index right hemicolectomy for CD coded in HES. This included surgery within 30-days of index operation and those at risk of multistage elective procedures within one year of index surgery, which were excluded from the main analysis. A further analysis using multivariable logistic regression was undertaken to assess the risk of undergoing a further surgery at the anastomotic site by 5-years in those with at least 5-years follow-up. The covariates described above were included in this model as well as the coding of colonoscopy 6-12 months following index right hemicolectomy.

Statistical analyses were carried out using STATA SE v15 [19]. P-values of <0.05 were considered statistically significant.

Ethics

HES data is available under data sharing agreements with NHS Digital for the purpose of service evaluation. Ethics approval is not, therefore, required. HES data was granted by the Health Informatics Request Review Group at University Hospitals NHS Foundation Trust: UHB Registration number CARMS-14875.

Results

Cohort characteristics

Between 1st Jan 2007 and 31st Dec 2016, 14,517 patients were identified with a CD diagnostic code and a first surgical code for right hemicolectomy. 12,230 patients were eligible for the study following exclusions. Median follow-up was 5.9 (IQR 3.6-8.6) years, contributing 74,960 person years at risk. 1,367 (11.2%) patients had a further surgery before the end of follow-up that was not an elective staged procedure within 1-year of index right hemicolectomy (199) or took place within 30-days of index procedure (306) and therefore considered valid for inclusion in further analysis (Figure 1). 55.2% (6,755) of patients were female and the median age was 36 (IQR 26-49) years. 35% of patients were aged from 18-29 years and 5% of patients were 70 years or older. 88.2% (10,792) had a white ethnicity code, 2.8% (346) were coded as Asian, 3.3% (409) were coded as other minority ethnicities and 5.7% of patients were not coded for ethnicity. 94.1% (11,510) of patients had no other comorbidities as defined by a Charlson score of zero. 1.9% of patients had a valid further surgery code within one year of their index operation. By 5-years 9% and by 10-years 16.9% of the right hemicolectomy cohort had undergone at least one further operation at the anastomotic site. Patient demographic characteristics are shown in Table 1.

Selection Bias

Univariate analyses comparing the sex, age, ethnicity, deprivation quintile and comorbidity categories of included and excluded patients were carried out (Appendix 3). Included patients were more likely to be female and have higher levels of deprivation. Excluded patients had a higher proportion with comorbidities and were older compared to included patients. No difference was observed between ethnicity for included and excluded groups.

Index surgical details and risk of further surgery

The number of index right hemicolectomies for Crohn's disease (CD) in England increased from 1,063 in 2007 to 1,317 in 2016, a 2% average annual rise. In those patients with at least 5 years of follow-up, further surgery fell from 185 procedures in 2007 to 109 procedures in 2013.

Using ONS data, the adult population of England for each index surgery inclusion year was recorded. CD prevalence in England for each year from 2007 to 2016 was used to estimate the yearly CD population in England. CD prevalence increased from 0.3% to 0.4% over this period. Index right hemicolectomy procedures fell from 6.90 to 5.96 per 1,000 patients with CD between 2007 and 2016 ($p<0.001$) (Appendix 4). Changes in index surgical rates per 1,000 CD patients during elective or emergency admissions were similar over the period with 4.20 to 3.52 ($p=0.002$) and 2.69 to 2.44 ($p=0.003$) respectively. CD prevalence and changes in index surgery rates over the study period are shown in Figure 2. The age of patients undergoing right hemicolectomy in England did not change over the study period (data not shown).

Within one year of index right hemicolectomy, 232 (1.9%) patients had had a further surgical resection at the site of the index operation, with a median time to further surgery of 229 (IQR 126-286) days. During study follow-up (range 2-12 years), 1,367 (11.2%) patients had a further surgical resection at the site of the index operation with a median time to further surgery of 1,064 (IQR 456-1,922) days or 2.9 years. Most index surgery was performed on an elective admission (59%), as was also the case for further surgery overall (63%). However, 50% of further surgery performed within one year of index surgery was performed on an emergency admission.

A Cox proportional hazards analysis of time to further surgery is shown in Table 2. Those in the older age quintile (54 and over) were at reduced risk of further surgery compared to the youngest age quintile (adjusted hazard ratio (aHR) 0.81 (95% CI 0.67-0.97), $p=0.022$) and those with an index right hemicolectomy performed as a laparoscopic procedure had an 18% reduced risk of further surgery (0.82 (0.73-0.93), $p=0.003$). Those in the two least deprived quintiles were at significantly lower risk of further surgery compared to the most deprived quintile (quintile 4: aHR 0.80 (0.68-0.95), $p=0.009$; quintile 5: aHR 0.79 (0.66-0.94), $p=0.007$). Those with an elective index surgery admission were at 27% lower risk of further surgery than those with an index right hemicolectomy during an emergency admission (aHR 0.73 (0.65-

0.82), p<0.001, Figure 3). Patients with a history of perianal surgery were at increased risk of further surgery (1.49 (1.29-1.72), p<0.001. Patients with a comorbidity score of ≥5 had an increased hazard of further surgery compared to patients with a score of zero (aHR 1.38 (1.03-1.85), p=0.032). Comorbidity scores of ≥5 were mainly seen in the two oldest quintiles (85%) and the median time to further surgery in the highest comorbidity group was 637 (IQR 328-1,274) days compared to 1,089 (465-1,974) days for the low comorbidity group. Other age groups, sex, provider right hemicolectomy volume for CD and ethnicity were not associated with time to further surgery. Not all patients had equal follow-up time, nevertheless, when followed from index right hemicolectomy as 3-year eras (2007-9, 2010-12, 2013-15), a separation in the proportion of further surgery emerged, Figure 4. Globally a difference between curves was observed, log rank test p = 0.036. When stratified, a significant difference between the earliest and latest eras was observed (2007-09 & 2012-15; p = 0.009), though not between the latest two eras (2010-12 & 2013-15; p = 0.560).

Sensitivity analysis

1,872 (15.3%) patients underwent further surgery that was included in the sensitivity analysis (14.5% female and median age 34 (26-47) years). Factors associated with an increased risk of further surgery included higher comorbidity score and previous perianal surgery in keeping with the primary analysis. Factors associated with a reduced risk of further surgery included those in the least deprived quintile, those who had index laparoscopic surgery or elective index surgery. However, unlike the primary analysis, no significant age relationship was identified. The demographic details and the Cox proportional hazards analysis can be found in appendix 5.

5-year follow-up cohort

8,239 patients (55.8% female and median age 36 (26-49) years) were found to have at least 5-years of follow-up (index surgery from 2007-2013). 747 (9%) patients had undergone further surgery at the anastomotic site by 5-years and the median time to further surgery was 2.88 (1.04-3.58) years. Factors associated with an increased risk of further surgery by 5-years were prior perianal surgery (odds ratio 1.48 (1.20-1.83), p<0.001), colonoscopy between 6-12 months post right hemicolectomy

(1.45 (1.22-1.74), p <0.001) and a Charlson comorbidity score of 1-4 compared to a score of 0 (1.34 (1.07-1.67), p = 0.012). Factors associated with a reduced risk of further surgery included having an elective index procedure (0.78 (0.67-0.92), p=0.002), index laparoscopic surgery (0.79 (0.66-0.94), p=0.010) and being in the oldest compared to the youngest quintile (0.74 (0.57-0.95), p=0.017). The demographic details and the logistic regression analysis of patients with at least 5-years of follow-up can be found in appendix 6.

Post-Surgery Colonoscopy rates

From 2007 to 2016 colonoscopy rates following a right hemicolectomy in CD patients increased in England from 35.0% to 61.3% of cases during the 24-month period following surgery. The number of colonoscopies per month following index surgery are shown in Figure 5**.** In the 6-12-month period following index right hemicolectomy, colonoscopy rates increased from 13.7% in 2007 to 29.0% in 2016 (Table 3). This accounts for 21.9% of patients undergoing right hemicolectomy for CD over the study period. 78.1% of patients did not have a colonoscopy within the 6-12-month period. 40.1% of patients did not have a colonoscopy within this 6-12-month window but did have a potential explanation why this may not have occurred, including a valid further surgical procedure, relevant illness coded, or they had died. This leaves a significant number of patients without a valid explanation for not having a post-resection 6-12 month colonoscopy as recommended (41.4% of patients). When provider volume of index right hemicolectomy for CD was compared to 6-12 month colonoscopy adherence, a four-fold difference between the 5th and 95th percentile provider was seen. This was consistent for both unadjusted data and when further surgery, patient death, potentially relevant illness or colonoscopy performed between 3 and 18 months were taken into account (Figure 6 and Appendix 7). When those patients who did not have a colonoscopy within 2 years of surgery were reviewed (6,012), 30% were coded as having missed a gastroenterology appointment without prior cancellation.

Between 3-18 months following index surgery 520 (4%) patients had some form of imaging modality (MRI abdomen/CT abdomen or colon /barium enema/capsule endoscopy), 60% of which also had a colonoscopy within this time period. 202 (40%) patients with imaging between 3-18 months post-index surgery had a colonoscopy within 6-12 months of index surgery while 60 (12%) had imaging and colonoscopy within 6-12 months.

Between 2007 and 2017 all colonoscopies coded in HES increased from 470,648 to 763,661 – a 69% increase over the study period. This equates to a rise of 916 to 1,373 per 100,000 population based on Office for National Statistics midyear population estimates for 2007 and 2017 – an increase of 50% when adjusted for population change [18]. In those with a diagnosis of CD, colonoscopies increased from 11,517 to 23,997 – an increase of 108% (data shown in Appendix 8).

Validation

All admissions at Sandwell and West Birmingham NHS trust hospitals with an ICD-10 code for CD (K50*) and a surgical code for right hemicolectomy (Appendix 1), excluding any cancer code, were examined between the period of Dec 2015 to Dec 2017. All 65 cases identified were accurately coded as CD when compared to the electronic patient record. 64 (98%) were correctly coded for the surgical procedure when compared to the operating notes. Colonoscopy within 6-12 months of surgery in these patients was coded with greater than 75% agreement between HES data and hospital patient records (figures omitted due to low numbers to preserve patient anonymity). Although these figures are small and the period of time short, previous validation of colonoscopies in HES have been shown over a longer period to be very robust with >95% congruency [20].

Discussion

Surgery in CD is the rule rather than the exception, with most patients having an intestinal resection during the course of their disease [3,4]. It is a valuable option for patients struggling with symptoms despite optimal medical management [11,21]. Resection of terminal ileal and right colonic disease is the most common major surgery performed in those with CD [22,23]. Previous findings suggest that surgery is common in the early period following diagnosis and may be a manifestation of an aggressive disease course as well as diagnostic delay [24,25]. Preventing the need for surgery and subsequent surgery is an important goal of CD therapy. Although when a decision is taken to operate, this is often the best choice for the patient at the time, earlier intervention may change the natural history of the disease and prevent the risks of surgery to a patient.

Index surgery increased over the study period in England. However, when CD burden in England was considered a relative decline was observed, both in elective and emergency settings. Stable and increasing numbers of surgery for CD have been noted previously [26,27], but when the increasing prevalence of this disease is accounted for, others have also found a fall in rates of surgery among CD patients [28]. Indeed, in England, Ahmed et al. have previously shown, using HES data, that as a proportion of CD hospital admissions, all types of major abdominal surgery for CD have fallen over time [29]. A UK primary care study, looking at first and further resectional surgery over 10 years from CD diagnosis and index surgery, respectively, found a significant fall in surgical risk [7]. Historically, surgical rates have fallen significantly, even before the advent of biologic medications [5,30]. The reasons for this relative decline in surgery is likely to be multifactorial with both the impact of better medical therapy, falling smoking rates and better systems of management as well as earlier diagnosis and milder disease being diagnosed playing key roles [31,32]. Evidence of this may be seen in a study from Canada where surgery was adjusted for CD prevalence. In that case an overall fall in surgery was seen over time due to a decline in emergency surgery whereas elective surgery was seen to increase over the same period [28]. Furthermore, others have correlated a fall in first resectional surgery with the use of immunomodulators [33] and a preventative strategy of using post-operative thiopurine use was clearly shown to be effective, for example, in smokers in the

TOPPIC trial [24,34]. Biologic therapy was not included in this study because self-administered drugs such as adalimumab are not captured in HES, however, biologics have also been linked to a fall in surgery. Certainly, in observational studies, their increasing use has correlated with the observed fall in surgical rates [5]. Their real-world use in terms of timing of initiation, patient selection and confounding in terms of disease severity and loss of response over time has, however, meant that strong evidence of a long-term reduction in surgery rates has been challenging to demonstrate when compared to their impressive performance in short randomised control trial follow up periods [35–37]. Although causality cannot be ascribed to the differences in further surgery risk observed between eras in the current study (Figure 4), it is of interest that significant differences were observed between periods before and after the introduction of maintenance anti-TNF therapy for CD in England.

In the current study, further surgery at the site of the anastomosis was 1.9% at 1 year and 11.9% over all follow-up. Previous studies looking at the risk of surgery in CD patients have highlighted female sex, smoking and ileal disease as significant predictive factors [38,39]. Further surgery has also been associated with continued smoking, previous surgery, the need for steroids or antibiotics and penetrating disease behaviour [8,11,40]. Females made up 55% of the cohort as might be expected given the higher prevalence of CD seen in females [17]. We found no significant reduction in risk of further surgery for females. The phenomenon that males have been shown to be at increased risk of major abdominal surgery in CD has, however, been previously observed [40], and we have previously shown a protective association of female sex in those with acute ulcerative colitis in relation to surgical intervention [41]. It may be that this study was underpowered to demonstrate a significant difference in the sexes. We speculate that although studies comparing acute illness outcomes between the sexes have found contradictory results, several factors are likely to be potentially important, including differences in physiological response to illness, disparity in smoking rates and differences in willingness to undergo surgery related to fertility and cosmesis [42–44].

A reduced risk of further surgery observed in patients from less deprived quintiles may reflect educational levels, as lower education has previously been associated with a more severe disease course. Lower deprivation levels may also be considered a surrogate for smoking. However, in a healthcare system such as the National Health Service, where access to care is not dependent on income, concordance with medical plans and medication regimes may be the cause of such findings [45]. Medication and smoking data is, however, not available in HES which limits this study given that smoking has been shown to adversely affect the natural history of CD [46,47]. The large multicentre TOPPIC trial found that post-operative thiopurine use reduced recurrence of CD in smokers and demonstrated the negative impact of smoking on clinical CD course [34]. Associations found with regards to sex and deprivation may then be confounded by a patient's smoking status. The factor most strongly associated with risk of further surgery in the current study was the admission method for index surgery. Those presenting electively had a reduced risk of further surgery which likely reflects the phenotype of the disease as well as better management processes for some patients and may further relate to educational levels and management adherence.

Although the age groups for analysis were banded into quintiles and so older age encompassed those over 54 years of age, 13% of index surgery patients were 60 or older and 19% of these underwent further surgery. These numbers are relatively small though they are an important minority given the inherent risks associated with major surgery and the physiological changes that come with age. Bernell et al reported that in their cohort of 907 patients with ileocaecal CD, in those who underwent surgical resection, 28% and 36% had recurrent disease at 5 and 10 years respectively. The risk of recurrence was lowest in those of older age [48]. Similarly, in the current study, older patients, compared to the youngest, were associated with a lower risk of further surgery. This may reflect a less severe disease course following index surgery. The phenomenon of autoimmune "burn-out" where a vigorous and damaging immune response observed in younger patients is not seen to the same extent due to an aging immune system may be pertinent here [49]. Indeed, the behaviour of CD in the elderly is often different, with reduced penetrating disease and predominance of colonic inflammation [50]. It should be noted that those with elderly onset and aging patients with IBD are not one and the same. Surgery may be a preferred option in the elderly when powerful immunosuppression is the alternative. In the largest cohort study of elderly IBD, CD ran a more benign course and most patients were never exposed to immunosuppressant medications [51]. Uniquely for this population, the study described a strong inverse relationship between systemic corticosteroids and risk of surgery, in line with the inflammation predominance of the disease in this cohort.

The increase in colonoscopy in the period following resectional surgery over the study period may reflect not only a strong evidence base and more recent guidelines but also accessibility, capacity and lowering of thresholds for colonoscopy in these patients. Despite relatively lenient mitigating reasons in the current study for not having a postoperative endoscopy, large numbers of patients had no obvious reason for not undergoing colonoscopy, with potential alternative imaging modalities coded in a tiny proportion of patients. However, other reasons that are not captured in hospital records are also likely to play a mitigating role and limit this approach. It is important to note that the association between colonoscopy and index surgery is temporal and may be symptom triggered, as opposed to scheduled post-surgery. In the logistic regression analysis examining the risk of further surgery in those with at least 5 years of follow up, colonoscopy at 6-12 months was associated with a 45% increased risk of further surgery suggesting that symptoms warranting surgical intervention were investigated. It is anticipated that in future, ileocolonoscopy post-surgery will increase in line with guideline recommendations and lead to a further fall in surgical intervention through early medical therapy for recurrent disease. The demographic of patients with CD is often young adulthood, and we have shown high rates of non-attendance at gastroenterology appointments in this cohort which may reflect increased mobility and risky behaviours in this group which would further compound reduced colonoscopy post-surgery. Currently in practice in some settings, though not as well validated or sensitive as colonoscopy [52], are magnetic resonance enterography (MRE) and ultrasonography which may be preferred by patients over colonoscopy. Although ultrasound for IBD is not specifically coded in HES and was therefore not investigated, we found that 520 patients had imaging investigations (MRI, CT and capsule endoscopy) between 3-18 months post-surgery, however, few had these imaging modalities in place of colonoscopy. Biomarkers may play a greater role in detecting recurrence of disease in future and are likely to be more acceptable to patients. Colonoscopy is expensive and faecal calprotectin has been shown to correlate with endoscopic mucosal activity, beyond clinical relapse, which is in keeping with how endoscopic recurrence will often not correlate with the symptomatology of individuals [8,53].

The HES database has significant strengths in terms of data capture of demographics, diagnoses, admission method and procedures for the whole of England, however some important data pertinent to CD is not available. Smoking, disease severity and extent, and medications are not captured, and these have been shown to influence the course of CD and the subsequent need for surgery [54].

Although the validation of surgical coding in our local centre was excellent, there may be differences in quality across hospitals which would also affect colonoscopy coding. It should be noted that coding of procedures allows hospitals to recoup costs and so there is an incentive to ensure coding of procedures is done to a high standard. Unfortunately, endoscopic balloon dilatation or stricture stenting is not well coded in HES and is an important limitation. These techniques have been shown to have low complication rates and may provide long-term relief of symptoms in some patients and delay the need for surgery in others [55,56]. Furthermore, radiological investigations may have been used in patients who did not undergo endoscopy, and this was not captured in the study. Despite these limitations, this study has highlighted the English experience of recurrent surgery following right hemicolectomy.

We have shown that although right hemicolectomy for CD has increased over a 10-year period, there has been a consistent fall given the overall proportion of CD patients in the population. Older patients are at the lowest risk of further surgery, but those with higher comorbidity who undergo further surgery, undergo this surgery in a shorter period of time than those without comorbidities. Those with lower deprivation levels had a reduced risk of further surgery, which may reflect medication and management adherence as well as smoking status in high deprivation groups. The factor most associated risk of further surgery was the admission method of index right hemicolectomy. Those with emergency presentation had the highest risk association which likely reflects severity of disease. Surgery is the right option for many and the focus of clinicians should be on their patients' goals, which will include and may prioritise quality of life [21,57]. As medical options increase, the decision for surgery must be carefully weighed and not delayed in those who would benefit given the higher risk of complications in those with poor physiological reserve and recent immunosuppression exposure [58]. Clinicians managing CD following surgery should be mindful of their patients' understanding of their disease and subsequently compliance with management plans.

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Table 1: Demographic characteristics of study patients

Demographic		Patients N (%)	Further surgery (by 1-year) N (%)	Further Surgery N (%)
Total		12,230 (100)	232 (1.9)	1,367 (11)
Follow-up years - Median (IQR)		5.9 (3.6-8.6)		
Sex	Male	5,475 (44.8)	118 (2.2)	646 (11.8)
	Female	6,755 (55.2)	114 (1.7)	721 (10.7)
Age - Median (IQR)		36 (26-49)	34 (25-45.5)	34 (25-46)
Age quintile	18-24	2,478 (20.3)	54 (2.2)	305 (12.3)
	25-31	2,459 (20.1)	47 (1.9)	291 (11.8)
	32-41	2,550 (20.9)	53 (2.1)	308 (12.1)
	42-53	2,428 (19.9)	48 (2.0)	258 (10.6)
	54+	2,315 (18.9)	30 (1.3)	205 (8.9)
Age deciles	18-29	4308 (35%)		370 (9%)
	30-39	2704 (22%)		369 (14%)
	40-49	2232 (18%)		282 (13%)
	50-59	1414 (12%)		191 (14%)
	60-69	993 (8%)		100 (10%)
	70+	579 (5%)		55 (9%)
Ethnicity	White	10,792 (88.2)	216 (2.0)	1223 (11.3)
	Asian	346 (2.8)	*	35 (10.1)
	Other minority ethnicities	409 (3.3)	*	41 (10.0)
	Unknown	683 (5.6)	9 (1.3)	68 (10.0)
Charlson comorbidity score	0	1,1510 (94.1)	214 (1.9)	1,295 (11.3)
	1-4	308 (2.5)	7 (2.3)	29 (9.4)
	5+	412 (3.4)	11 (2.7)	43 (10.4)
Deprivation quintile	1 (Most Deprived)	2,655 (21.7)	47 (1.8)	335 (12.6)
	2	2,699 (22.1)	55 (2.0)	305 (11.3)
	3	2,496 (20.4)	41 (1.6)	275 (11.0)
	4	2,282 (18.7)	42 (1.8)	240 (10.5)
	5 (Least Deprived)	2,098 (17.2)	47 (2.2)	212 (10.1)
Index surgery admission method	Emergency	4,924 (40.3)	119 (2.4)	661 (13.4)
	Elective	7,225 (59.1)	107*	696 (9.6)
Further surgery admission method	Emergency	-	115 (49.6)	504 (36.9)
	Elective	-	107*	857 (62.7)
	Unknown	-	*	6 (0.4)
Year of index surgery	2007	1,063 (8.7)	26 (2.4)	185 (17.4)
	2008	1,100 (9.0)	31 (2.8)	204 (18.5)
	2009	1,149 (9.4)	31 (2.7)	175 (15.2)
	2010	1,189 (9.7)	23 (1.9)	161 (13.5)
	2011	1,226 (10.0)	14 (1.1)	127 (10.4)
	2012	1,274 (10.4)	20 (1.6)	155 (12.2)
	2013	1,292 (10.6)	28 (2.2)	109 (8.4)
	2014	1,263 (10.3)	24 (1.9)	114 (9.0)
	2015	1,357 (11.1)	18 (1.3)	73 (5.4)
	2016	1,317 (10.8)	17 (1.3)	64 (4.9)
Provider volume of right hemicolectomy	Low (1-54)	1,556 (12.7)	38 (2.4)	173 (11.1)
	Medium (55-89)	3,801 (31.1)	76 (2.0)	404 (10.6)
	High (90+)	6,873 (56.2)	118 (1.7)	790 (11.5)
Colonoscopy timing post index surgery	0-3 Months (Very Early)	205 (1.7)	8 (3.9)	32 (15.6)
	3-6 Months (Early)	1,120 (9.2)	24 (2.1)	123 (11.0)
	6-12 Months (On Time)	2,681 (21.9)	60 (2.2)	345 (12.9)
	12-18 Months (Late)	1,395 (11.4)	37 (2.7)	190 (13.6)
	18-24 Months (Very Late)	817 (6.7)	24 (2.9)	123 (15.1)
	Later or Never	6,012 (49.2)	79 (1.3)	554 (9.2)
Prior perianal surgery		1,475 (12.1)	31 (2.1	230 (15.6)
Laparoscopic index surgery		4,587 (37.5)	78 (1.7)	385 (8.4)

*Patient numbers ≤5 supressed to maintain anonymity.

Table 2: Cox proportional hazards model of factors associated with further resectional surgery during follow-up at the site of previous right hemicolectomy for Crohn's disease

Demographic		Haz. Ratio	[95% CI]		P Value
Sex	**Male (Baseline)**				
	Female	0.93	0.84	1.04	0.198
Age quintile	**18-24 (Baseline)**				
	25-31	0.98	0.84	1.16	0.849
	32-41	0.99	0.85	1.17	0.945
	42-53	0.91	0.77	1.08	0.286
	54+	0.81	0.67	0.97	**0.022**
Ethnicity	**White (Baseline)**				
	Asian	0.80	0.57	1.12	0.197
	Other minority ethnicities	0.84	0.61	1.15	0.276
	Unknown	0.90	0.70	1.15	0.384
Charlson (comorbidity) score	**0 (Baseline)**				
	1-4	1.07	0.90	1.26	0.455
	5+	1.38	1.03	1.85	**0.032**
Deprivation quintile	**1 (Most Deprived) (Baseline)**				
	2	0.87	0.75	1.02	0.082
	3	0.86	0.73	1.01	0.072
	4	0.80	0.68	0.95	**0.009**
	5 (Least Deprived)	0.79	0.66	0.94	**0.007**
Index surgery admission method	**Emergency (Baseline)**				
	Non-Emergency	0.73	0.65	0.82	**<0.001**
Year of index right hemicolectomy	**2007 (Baseline)**				
	2008	1.15	0.94	1.41	0.163
	2009	0.99	0.80	1.22	0.890
	2010	0.94	0.76	1.17	0.599
	2011	0.79	0.62	1.00	**0.048**
	2012	1.08	0.87	1.36	0.476
	2013	0.84	0.66	1.08	0.169
	2014	1.05	0.82	1.35	0.674
	2015	0.78	0.59	1.04	0.089
	2016	0.92	0.68	1.24	0.577
Provider volume of Crohn's disease index right hemicolectomies (tertile)	**Low (1-54) (Baseline)**				
	Medium (55-89)	0.96	0.80	1.14	0.628
	High (90+)	1.02	0.87	1.21	0.771
Prior Perianal Surgery		1.49	1.29	1.72	**<0.001**
Laparoscopic Index Surgery		0.82	0.73	0.93	**0.003**

Table 3: Colonoscopy rates between 6 and 12 months of index right hemicolectomy by year of the study period

Index right hemicolectomy year	Colonoscopy 6-12 months (%)
2007	146 (13.7)
2008	168 (15.3)
2009	222 (19.3)
2010	228 (19.2)
2011	251 (20.5)
2012	296 (23.2)
2013	312 (24.1)
2014	330 (26.1)
2015	346 (25.5)
2016	382 (29.0)
Total	**2681 (21.9)**

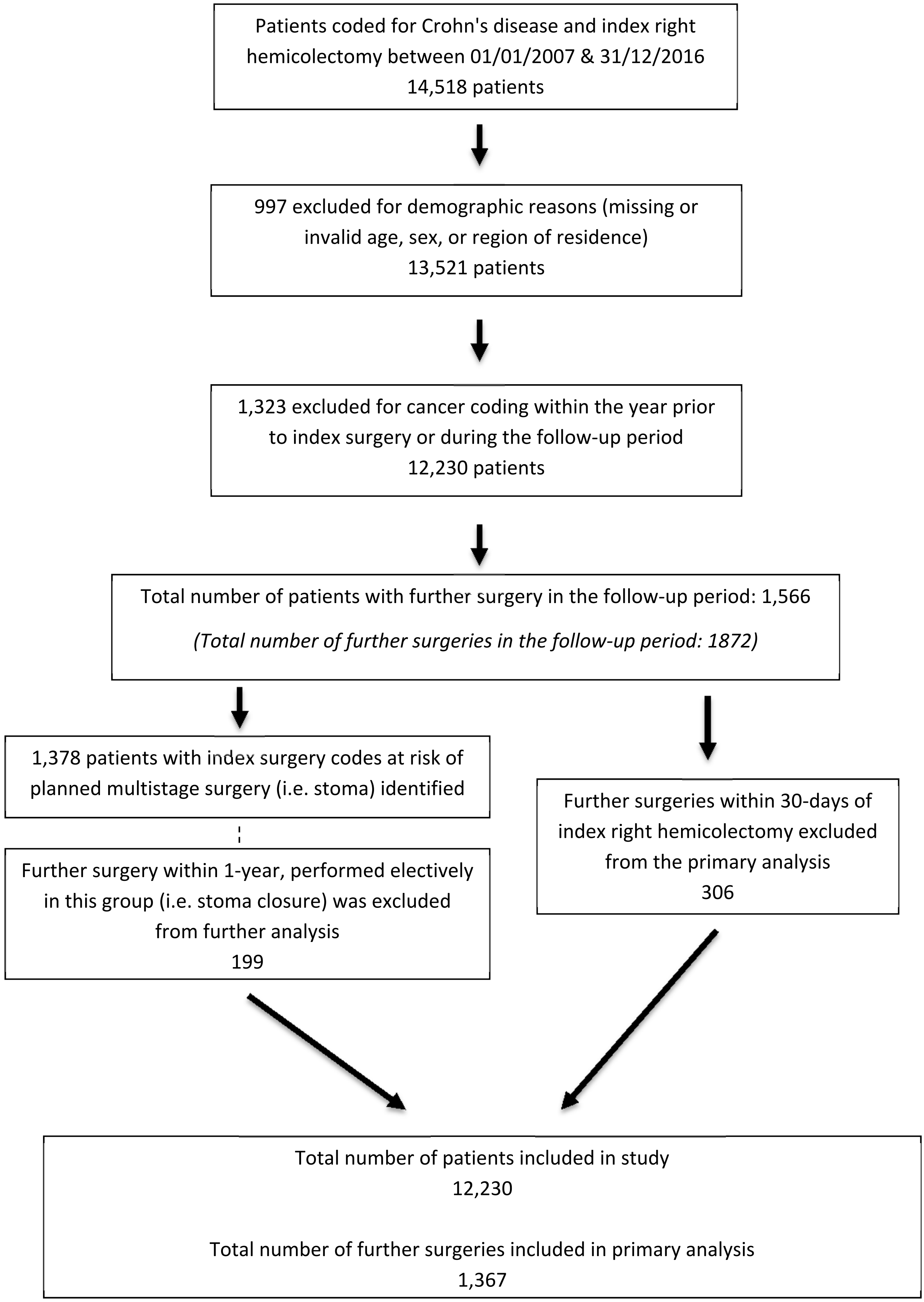

Figure 1. Study Flow Chart

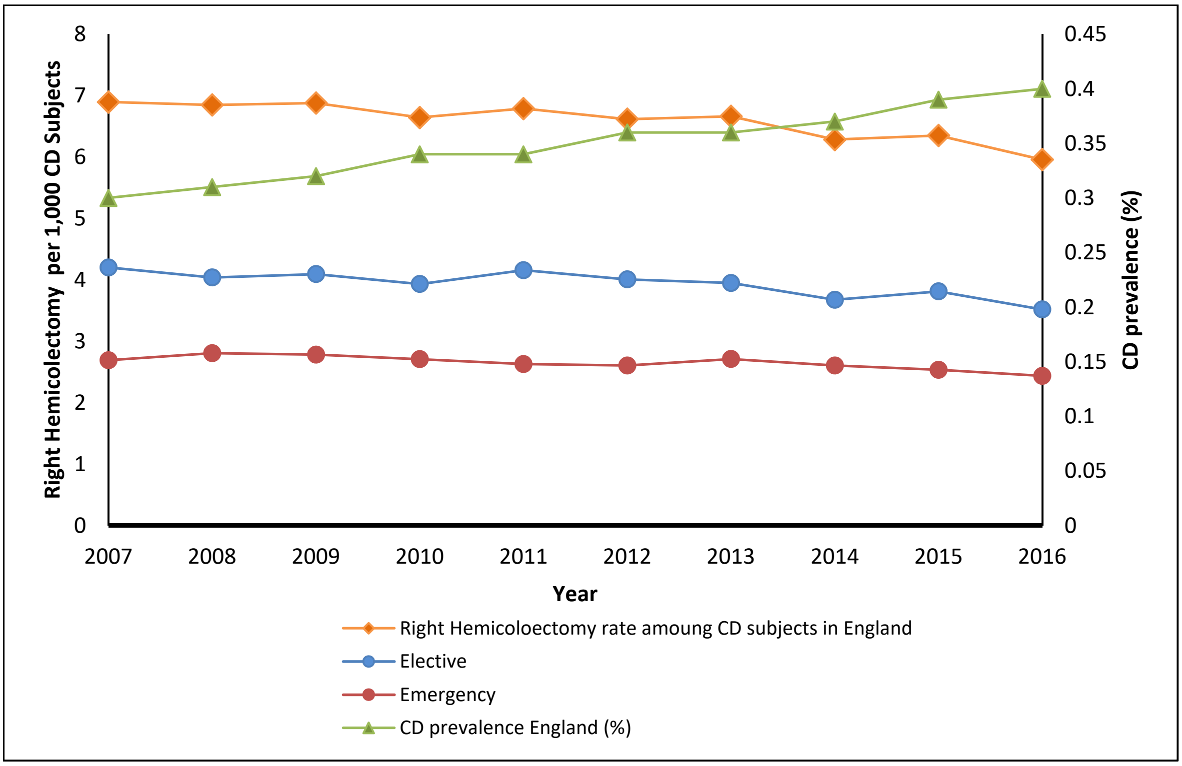

Figure 2. Change in rate of right hemicolectomy in comparison with prevalence of Crohn's disease in England

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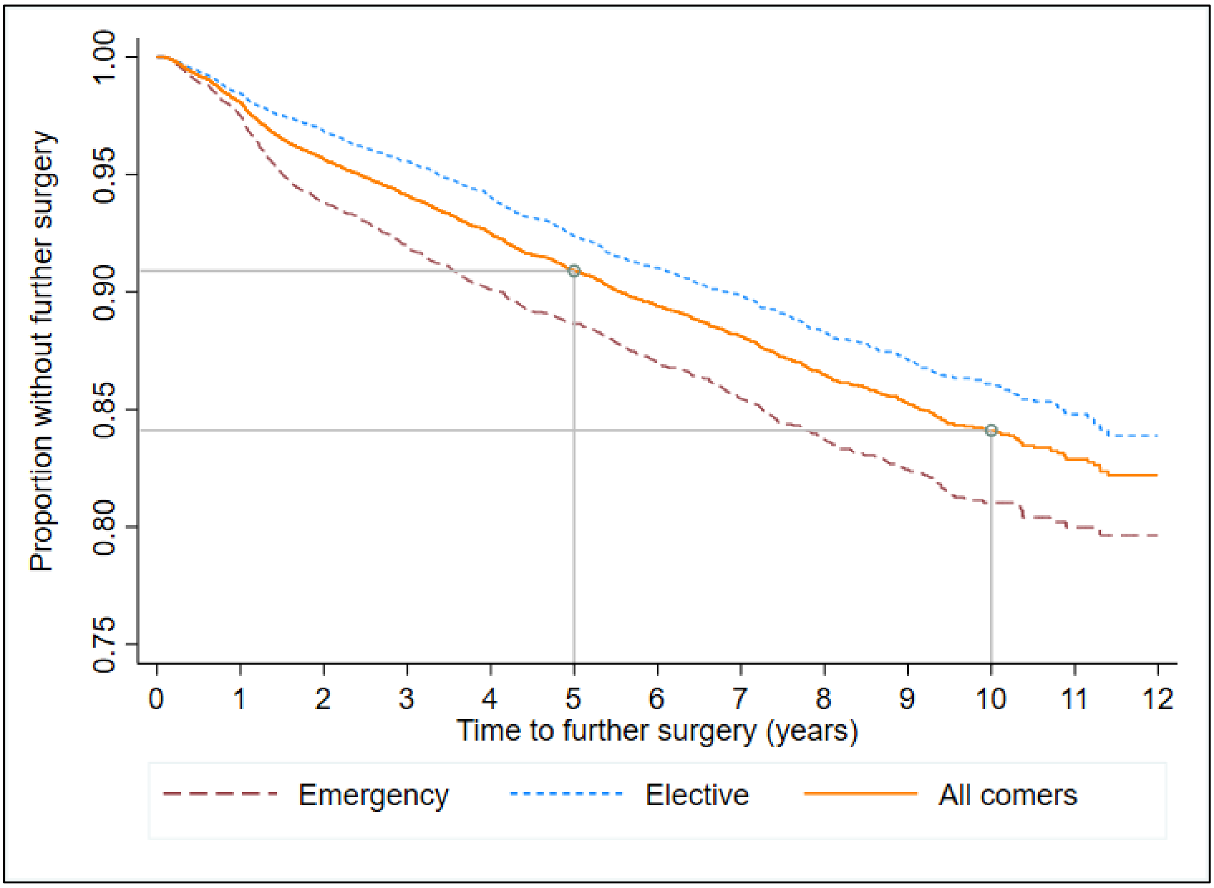

Figure 3. Kaplan-Meier analysis of time to further surgery dependent on index surgery admission method

639

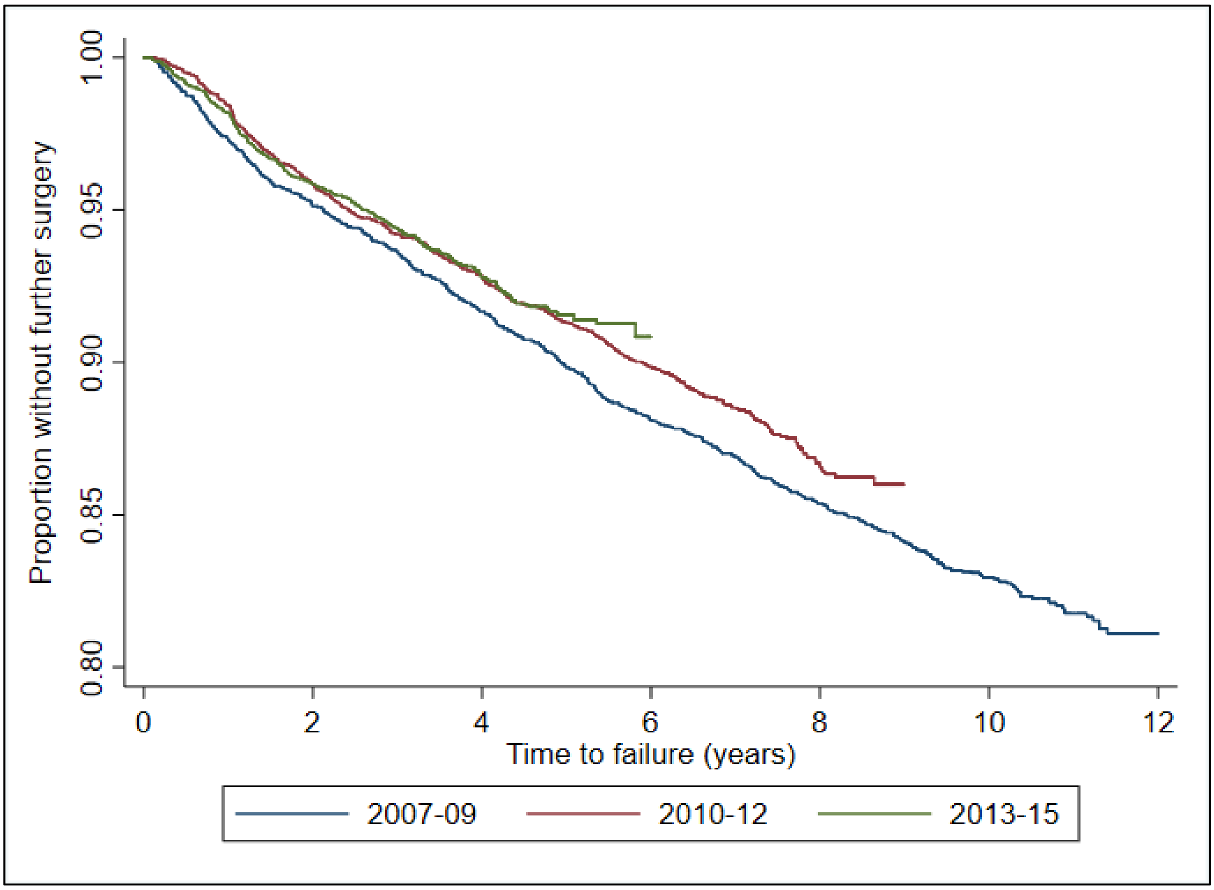

Figure 4. Kaplan-Meier analysis showing the proportion of patients from 3-year time periods of index right hemicolectomy who have further surgery.

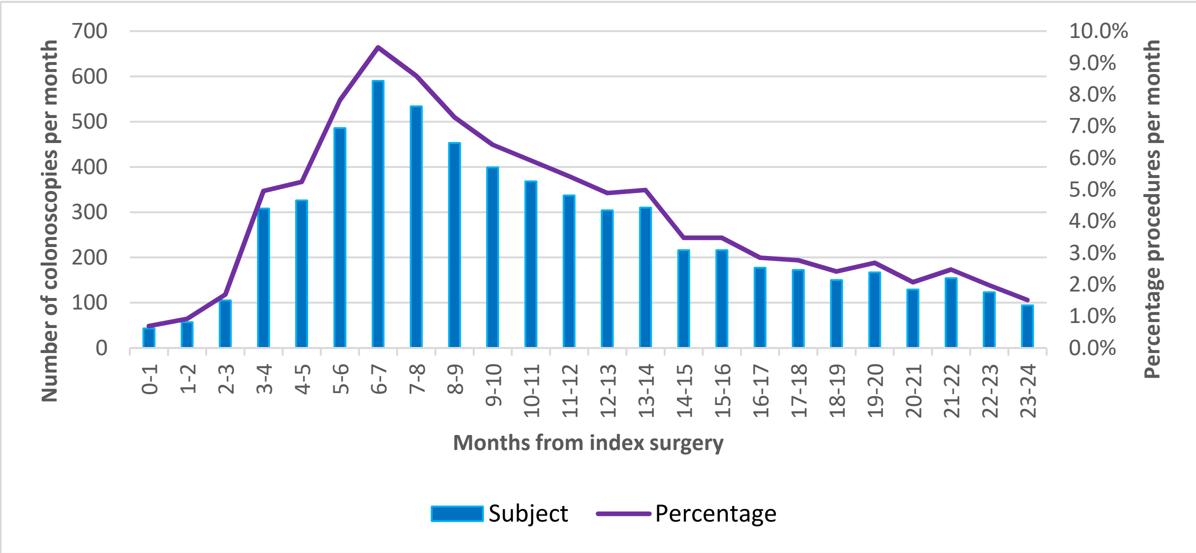

Figure 5. Colonoscopy numbers (%) per month following index right hemicolectomies

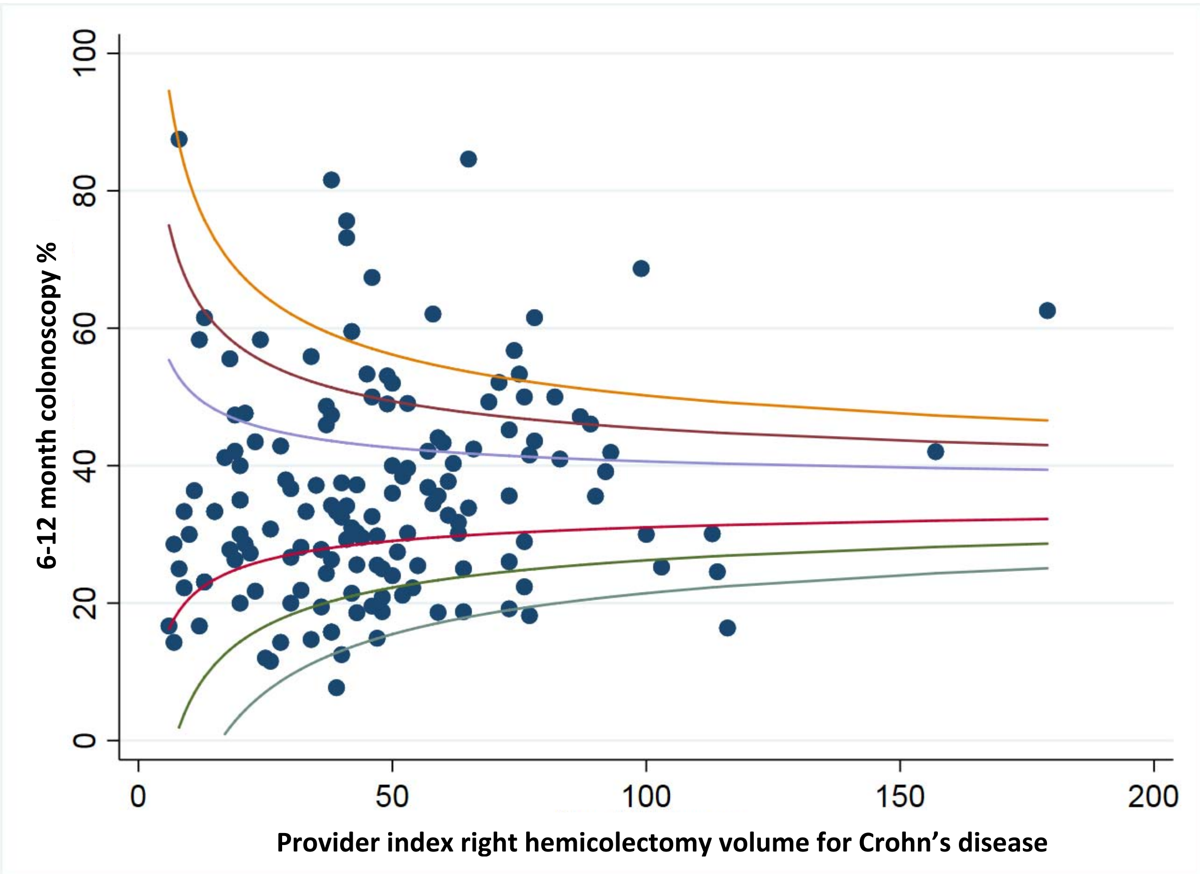

Figure 6. Funnel plot of provider volume of index right hemicolectomy for Crohn's disease by 6-12 month post-surgery colonoscopy adherence
(Lines show 1, 2 and 3 standard deviations from the mean)
(Adjusted for mitigating illness, further surgery, patient death and 3-18 month colonoscopy)

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Conflicts of Interests

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