Evelien M.J. Beelen

POSTOPERATIVE RECURRENCE OF CROHN'S DISEASE AFTER ILEOCOLONIC RESECTION

Epidemiology, prediction and prevention

Propositions associated with the thesis:

Postoperative Recurrence of Crohn's Disease after Ileocolonic Resection

Epidemiology, prediction and prevention

1. The risk of ileocolonic, small bowel and colon resections and re-resections in Crohn's disease patients has decreased substantially over the past decades, with the most significant decrease before 1999. *This thesis*

2. Timing of primary ileocecal resection in patients with Crohn's disease is not associated with a change of the disease course and should not be weighed in clinical decisions. *This thesis*

3. Postoperative clinical risk stratification and treatment with prophylaxis has an acceptable predictive value for endoscopic recurrence with limited improvement after incorporation of histologic assessment. *This thesis*

4. Further refinement of risk stratification is required to identify Crohn's disease patients at low risk of recurrence, to reduce overtreatment with prophylactic medication. *This thesis*

5. Postoperative prophylaxis with anti-TNF-α is superior to thiopurine therapy in the prevention of clinical and endoscopic recurrence in Crohn's disease patients. *This thesis*

6. Optimal care pathways bring gastroenterologists and surgeons together to provide best treatment practices in the perioperative phase, surgical phase, and postoperative phase. *Barnes et al. Clinical Gastroenterology and Hepatology 2020*

7. Improved prediction of disease course remains one of the major unmet needs in Crohn's disease management and a research priority in the field. *Noor et al. Lancet Gastroenterology and Hepatology 2020*

8. Er lijkt een mismatch te zijn ontstaan tussen wat een wet of richtlijn van de onderzoeker verlangt en wat daadwerkelijk bijdraagt aan veilig en kwalitatief onderzoek. *Werkgroep ontregel het onderzoek. Medisch Contact 2021*

9. To give our patients the best care and to reduce the chance of medical error, we must make sure we look after ourselves too. *Brennan et al. BMJ 2019*

10. The more I see, the less I know for sure. *John Lennon*

11. We are all in the gutter, but some of us are looking at the stars. *Oscar Wilde*

Evelien Beelen, 2022

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Epidemiologie, voorspellen en voorkomen

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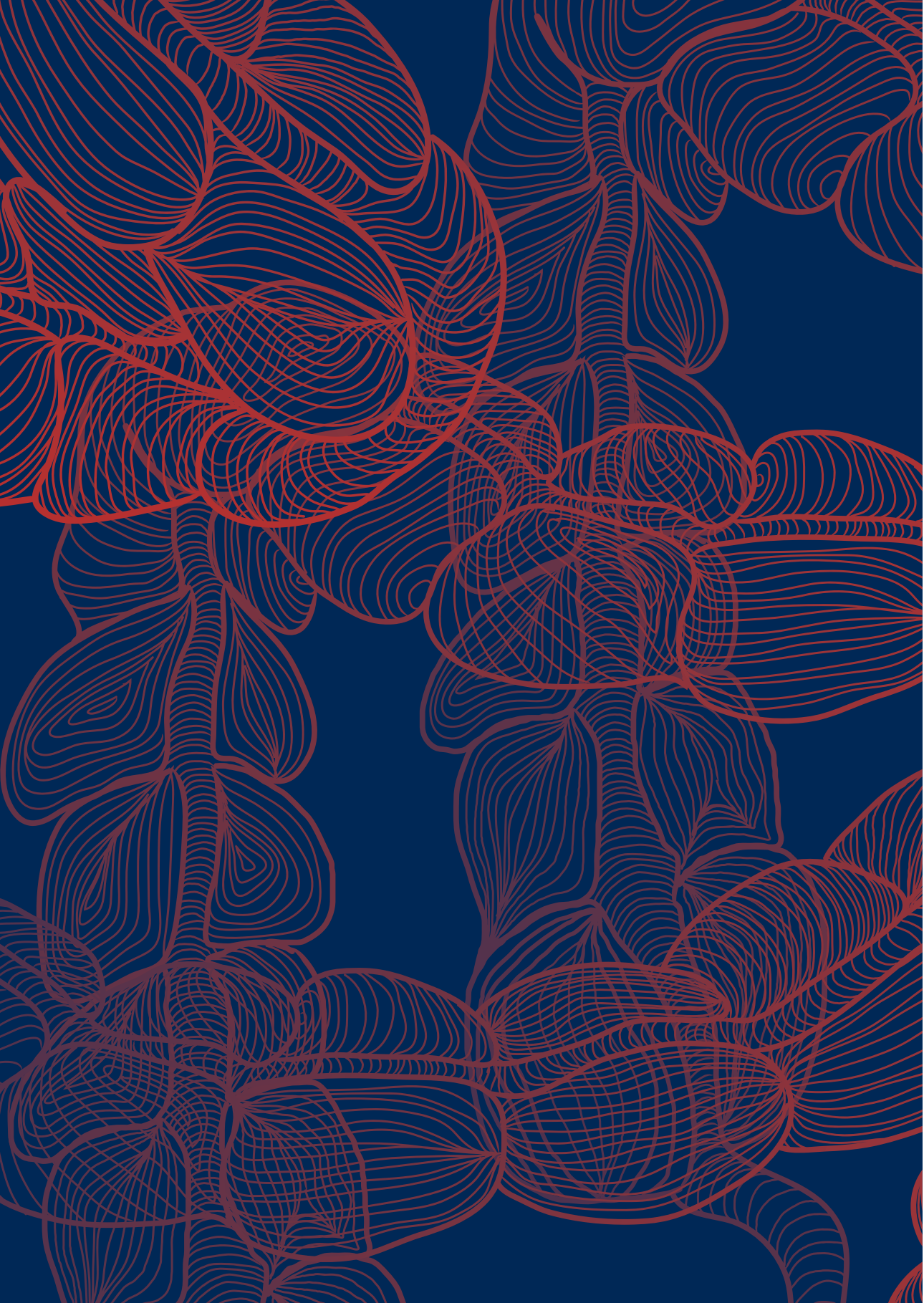


CHAPTER 1

General introduction and outline of this thesis

General introduction

Crohn's disease

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) which is characterized by a relapsing remitting disease course.[1] Prevalence is highest in Europe and North America. Reported prevalence rates in Europe vary from 1.5 to 322 cases per 100,000 person-years. The incidence of CD has risen over the past decades. Although prevalence rates are highest in high-income countries in Europe and North America, incidence rates are also increasing rapidly in newly industrialized countries in Asia, South America and Africa.[2-4] The exact etiology of CD is unknown. The most supported hypothesis is that CD originates from a combination of multiple factors e.g. environmental factors, genetic susceptibility and microbial alterations contribute to dysregulation of the immune response, and result in a self-perpetuating inflammation of the intestinal mucosa.[1, 5] Patients usually present with diarrhea and abdominal pain, but also systemic symptoms like fatigue and weight loss.[6] CD can occur anywhere in the gastrointestinal tract, but most commonly manifests in the ileum and colon. In addition to intestinal inflammation, many patients suffer from extra-intestinal manifestations, e.g. spondylarthropathy or uveitis can occur.[7] CD often has a progressive natural course, during which intestinal transmural inflammation leads to disease complications, including strictures and penetrating complications (fistula or abscess).[1, 8] CD is diagnosed based on a combination of clinical symptoms, endoscopic or radiologic lesions and histological findings.[6] Over the past decades, CD management goals have shifted from merely symptom control to inducing and sustaining deep mucosal remission, and thereby preventing development of complications.[9] CD treatment is largely based on medication inhibiting an inflammatory response. The current treatment arsenal consists of corticosteroids (budesonide, prednisone), immunomodulators (thiopurines and methotrexate) and biologicals (anti-TNFα, vedolizumab, ustekinumab). Small molecule compounds (e.g. JAK inhibitors filgotinib and upadacitinib) are in pipeline for CD treatment.[6, 9] Despite the rapidly expanding treatment options, a large portion of patients develop complications and require a surgical resection during the course of disease.[10, 11]

Intestinal resection in Crohn's disease

A large proportion of patients with CD will undergo intestinal resection during the disease course. In meta-analyses, bowel resection rates are estimated at 40-50% at 10 years after CD diagnosis.[11, 12] However, a pooled analysis specifically in patients diagnosed with CD in the 21st century showed a primary resection rate of 26.2% after 10 years.[12] Strictureplasty is a bowel-sparing alternative for resection in case of symptomatic stricturing disease of the small bowel. Preferably, strictures should be shorter than 10cm in length, however strictureplasty may also be considered for larger strictures.[13] Intestinal resection options for CD include small bowel resection, ileocecal or ileocolonic resection (ICR) and colectomy.

For colonic CD, effective surgical treatment options include segmental colectomy, subtotal colectomy and total (procto)colectomy. Important considerations for the type of colonic resection include the length and location of the affected bowel and quality of life of the patient. Segmental colectomy is considered in patients in whom one bowel segment is affected. For patients with more extensive colonic disease, subtotal colectomy or proctocolectomy should be performed. Although permanent ileostomy can be avoided by subtotal colectomy, higher postoperative complication and recurrence rates are reported compared to proctocolectomy.[14, 15] Formation of an ileo pouch-anal anastomosis after proctocolectomy is only performed in a selection of patients (i.e. highly motivated patients after thorough counselling, without small bowel disease and without history of perianal disease) as high complication and pouch-failure rates are reported.[16, 17]

The most frequently performed resection for abdominal CD is an ICR with one-stage or two-stage (after temporary ileostomy) ileocolonic anastomosis. ICR may provide relief of symptoms and induce a period of clinical remission in patients with ileal or ileocolonic CD. Furthermore, it may reduce long-term exposure to biologicals or immunomodulators.[18]

Historically, medical CD treatment is considered the first-line therapy. According to guidelines, primary resection is preferred in case of stricturing disease in absence of inflammation. Other indications include abdominal fistula, obstructive disease and disease activity that is refractory to medical therapy. To maintain bowel function (with regard to adequate absorbance of nutrients, electrolytes and fluid) extensive intestinal resection is preferably avoided.[17] The introduction and wide-spread use of immunomodulators and biologicals might have led to postponement of surgical resection, where ICR is considered a last resort therapy.[19] However, in patients with localized ileal or ileocecal CD, minimally invasive ICR could be performed earlier in the disease course. A landmark randomized controlled trial (RCT) showed that in patients with limited, non-stricturing CD, ICR can be considered a reasonable alternative to anti-TNFα therapy with regards to quality of life and costs-effectiveness after 12 months.[20-22]

Over the past decades, surgical techniques have developed. If feasible and expertise is available, laparoscopy is preferred over an open surgical approach, as postoperative complication rates are lower.[23] With regards to ileocolonic anastomosis, several meta-analyses were published. Although included studies are of variable quality, and some meta-analyses show contradicting results, overall consensus is that ileocolonic side-to-side anastomosis **(Figure 1)** is preferred over end-to-end anastomosis **(Figure 2)**, as fewer anastomotic leakage, shorter hospital stay, lower overall postoperative complications and lower recurrence rates are reported.[24-26] No difference between hand-sewn or stapled anastomosis was found.[27]

Figure 1. Side-to-side anastomosis[28]

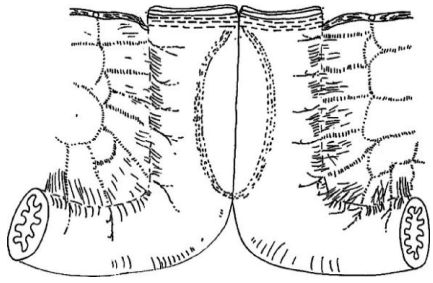
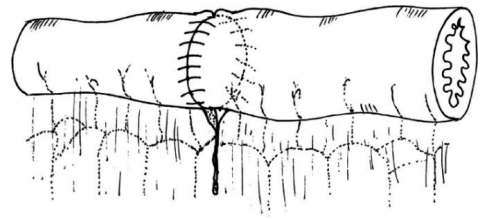
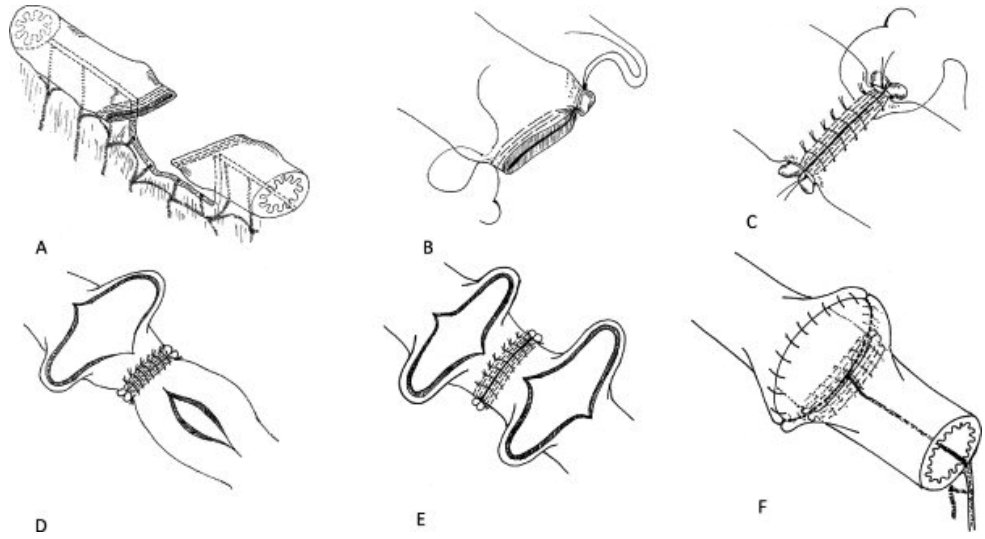


Figure 2. End-to-end anastomosis[28]



In 2011 the Kono-S anastomosis was first introduced, aiming to reduce anastomotic strictures, by formation of an anti-mesenteric, end-to-end, hand-sewn anastomosis.[29] Figure 3. Hypothetically, this method may lead to lower anastomotic recurrence in a few different manners. Firstly, the mesentery is divided close to the intestines to sustain blood supply and innervation to enhance healing. Figure 3A. Secondly, the mesentery is excluded from the anastomotic site by positioning it in the center of the posterior wall. Thirdly, the supporting column lowers mechanical distortions at the anastomotic site. Figure 3E and 3F. Recent reports described a significant reduction in postoperative CD recurrence in patients with Kono-S anastomosis as compared to traditional anastomosis.[30-33]

Figure 3. Kono-S anastomosis[28]



Postoperative recurrence

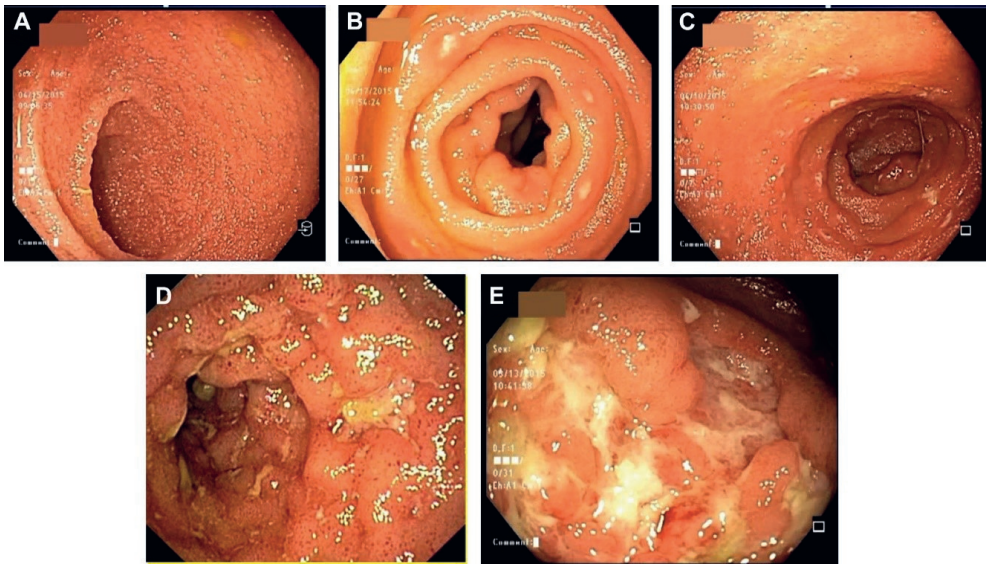
Surgical resection of the affected bowel segment is not a curative therapy for CD, and postoperative recurrence of intestinal inflammation after ICR is common. In literature,

postoperative recurrence is commonly divided into clinical, endoscopic and surgical recurrence.[34]

Clinical recurrence means the recurrence of symptoms compatible with active intestinal inflammation, and is preferably defined by a clinical score e.g. Harvey Bradshaw Index (HBI) or Crohn's Disease Activity Index (CDAI).[35, 36] Clinical recurrence occurs in approximately 10-38% of patients with CD within 1 year after resection.[34, 37] Since the correlation between clinical complaints and CD disease activity is limited, the validity of clinical recurrence as a marker of disease recurrence is questionable. Complaints after intestinal resection could have a different etiology such as bile salt diarrhea or bacterial overgrowth.[38]

Endoscopy is considered the gold standard for the diagnosis of postoperative recurrence and is used to monitor postoperative disease activity. Clinical recurrence is usually preceded by endoscopic inflammation. Endoscopic recurrence rates at 1 year after ICR are estimated at 35-85%.[34, 37, 39, 40] Rutgeerts et al. established an endoscopic score in 1990, to assess postoperative lesions in the neoterminal ileum and on the ileocolonic anastomosis after primary ICR. The Rutgeerts' score stratifies patients into 4 categories, i0-i4, according to the severity of the endoscopy lesions.[39] **Figure 4.**

Figure 4. Rutgeerts scoring index in the neoterminal ileum. i0, no lesions (A); i1, ≤5 aphthous lesions (B); i2, >5 aphthous lesions with normal intervening mucosa or lesions confined to the anastomosis (C); i3, diffuse aphthous ileitis with diffusely inflamed mucosa (D); i4, diffuse inflammation with large ulcers, nodules, and/or stenosis (E).[41]



Since hypothetically anastomotic ulcers have an ischemic etiology and may be less predictive of progressive CD, a modified Rutgeerts' score was developed. The modified Rutgeerts' score separates the Rutgeerts score i2 into two categories, differentiating between anastomotic lesions (i2a) and >5 lesions in the neoterminal ileum (i2b)[42] **Table 1** describes the modified Rutgeerts' score.

Table 1. The modified Rutgeerts score

i0	No lesions in the neoterminal ileum
i1	≤ 5 aphthous lesions in the neoterminal ileum
i2a	Lesions confined to the ileocolonic anastomosis
i2b	>5 aphthous ulcers with normal intervening mucosa, in the neoterminal ileum
i3	Diffuse aphthous ileitis with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, nodules, and/or stenosis

The Rutgeerts' score is widely used to assess postoperative endoscopic recurrence. It was established to predict the clinical disease course, however, it was never validated in an independent cohort and a cut-off for the definition of endoscopic recurrence is unclear. The predictive value of the Rutgeerts' score for the (long-term) postoperative disease course, especially after development of improved treatment strategies, remains uncertain. Furthermore, the clinical prognosis of Rutgeerts' score i2a vs i2b at early endoscopy is still a matter of debate. This could lead to inconsistency in decisions on the start of medical therapy. To assess early postoperative recurrence, guidelines recommend a standardized ileocolonoscopy between 6-12 months after ICR.[16, 43] A randomized trial demonstrated that early ileocolonoscopy and treatment step-up for recurrence resulted in lower postoperative CD recurrence at 18 months, as compared to conventional medical therapy alone.[37] Although not yet included in current guidelines or routinely used in clinical practice, promising results were published with regards to less invasive methods of postoperative monitoring, e.g. abdominal ultrasound, Magnetic Resonance Imaging (MRI) and fecal calprotectin.[44-49]

Surgical recurrence is defined as an intestinal re-resection. As recurrent intestinal resections are preferably avoided, surgical recurrence can be considered a robust and objective marker of the postoperative disease course. Surgical recurrence rates are estimated around 30-35% within 10 years after primary ICR.[12, 50]

Risk factors for postoperative recurrence

Several risk factors for postoperative recurrence in CD have been identified. Active smoking is the strongest and only modifiable, identified individual predictor of postoperative recurrence reported in clinical trials as well as cohort studies. A meta-analysis of 16 observational studies reported that smokers were at 2.0-fold increased risk of clinical and 2.5-fold increased risk of surgical recurrence.[51] Penetrating disease behaviour (Montreal B3

phenotype) was reported to be associated with postoperative recurrence (OR 1.5 for surgical recurrence).[52] However, in other studies penetrating disease behaviour was not significantly associated with recurrence, or was found to be protective of recurrence.[53, 54] Other clinical factors identified as risk factors of postoperative recurrence are prior intestinal resection in medical history and perianal disease location.[55, 56]

In addition to clinical factors, previous studies assessed histologic characteristics of the ileocolonic resection specimen to identify predictors of postoperative recurrence. A meta-analysis found microscopic inflammation of the resection margins to be associated with clinical (RR 1.26) and surgical (RR 1.87) recurrence. Furthermore, the presence of plexitis was associated with clinical (RR 1.34) and endoscopic (RR 1.31) recurrence. Finally, granulomas were found to be a risk factor for endoscopic recurrence (RR 1.37).[57] Another recent study could not identify individual histologic predictors for recurrence, however a combined definition of transmural inflammation was found to be associated with postoperative recurrence.[58]

The majority of the abovementioned risk factors are accepted by international guidelines as predictors of postoperative CD recurrence. However, data from prospective cohorts are scarce and available studies show contradicting results.[16, 34, 43] There is an unmet need for more accurate predictors of postoperative recurrence, to stratify high risk patients for targeted postoperative therapy.

Prevention of postoperative recurrence

Although the definitions of high-risk vary, available guidelines recommend starting prophylactic medical therapy in patients at high risk of postoperative CD recurrence.[16, 43] The arsenal of medication consists of several anti-inflammatory agents. Firstly, aminosalicylates or mesalamine; a pooled meta-analysis of 5 RCTs found an advantage of mesalamine as compared to placebo for the prevention of postoperative clinical recurrence.[59] However, the largest controlled trial did not demonstrate a difference in clinical relapse rate between mesalamine and placebo.[60] Secondly, corticosteroids are generally not prescribed in postoperative setting. Although a significant difference in the rate of endoscopic recurrence between patients receiving prophylactic oral budesonide as compared to placebo was found in two studies, a pooled analysis showed no difference in severe endoscopic recurrence after 12 months.[59, 61, 62] Thirdly, antibiotics, specifically metronidazole was previously shown to reduce endoscopic and clinical recurrence rates. However, the effect did not sustain after 1 year, and due to large numbers of reported side effects, antibiotics are not suitable for long-term use.[63] In addition, thiopurines have been studied in postoperative setting. In a large RCT, thiopurines overall were not superior to placebo in the prevention of postoperative recurrence. A significant advantage for thiopurines was only found in the subpopulation of smokers.[64] A meta-analysis showed thiopurines were superior to control arms in the

prevention of postoperative clinical and endoscopic recurrence.[65] Finally, infliximab, an anti-tumor necrosis factor (TNFα) agent, reduced endoscopic recurrence but not clinical recurrence at 76 weeks, as compared to placebo.[66] Trials directly comparing postoperative prophylactic agents are scarce. However, published network meta-analyses show an overall advantage of anti-TNFα over other therapies.[67-69] Current guidelines propose to start postoperative prophylaxis with thiopurines and/or anti-TNFα in high-risk patients and do not express a preference for one of both therapies.[16, 43] Other, newer therapies (e.g. ustekinumab, vedolizumab) have only been tested with regards to postoperative prophylaxis in retrospective setting. New data are awaited.[70, 71]

Outline of this thesis

As discussed above, surgery, including (segmental) intestinal resection, is a fundamental component of the interdisciplinary management of CD. The postoperative management of CD is challenging, as postoperative recurrence is common and re-resection rates are high. A knowledge gap exists regarding postoperative risk stratification and the optimal treatment strategy, limiting under- and over-treatment. The aim of this thesis is to enhance knowledge on the postoperative recurrence of CD after intestinal resection, with regards to epidemiology, prediction and prevention.

Part I: Epidemiology

The first part of this thesis focuses on epidemiology of intestinal resections in CD. The management of CD has considerably evolved over the past decades, with the development of new medication, new treatment targets and strict monitoring strategies, pre-operatively as well as postoperatively. The influence of these changes on resection rates in CD is unclear. In **chapter 2** we investigate time trends in intestinal resection and re-resection over the past decades in a nationwide cohort study in the Netherlands. **Chapter 3** concerns a short comment on the possible explanation for the observed decrease in intestinal resection rate in CD over time.

In addition to the risk of CD recurrence, other long-term complications may result from intestinal resections, and are mostly associated with malabsorption, such as nutritional deficiencies, osteoporosis and urolithiasis. The risk of cholelithiasis may also be increased, especially in patients with ileal disease location or ileal resection, possibly due to an altered gallbladder motility or bile salt malabsorption in the ileum. In **chapter 4**, the risk of cholecystectomy in CD patients after ileal resection is investigated in a nationwide cohort in the Netherlands.

Part II: Prediction

The second part of this thesis elaborates on the prediction of postoperative recurrence after ICR in CD. Evolving treatment and monitoring strategies might have led to postponement of ICR. However, ICR early in the disease course could induce a period of long-term clinical remission or prevent development of disease complications caused by chronic inflammation. Evidence on the optimal timing of ICR in CD is lacking. **Chapter 5** aims to investigate the association between timing of ICR, and identify other factors associated with, postoperative endoscopic recurrence, escalation of IBD medication or re-resection in a retrospective multicenter study.

When performing surgical side-to-side ileocolonic anastomosis, a blind ileal loop is created. In the Rutgeerts' score, the ileal blind loop is not taken into account and the prognostic value of isolated lesions in the blind loop is unknown. In **chapter 6**, we investigate the postoperative prognosis after isolated ileal blind loop inflammation during postoperative ileocolonoscopy.

In addition to clinical risk factors, histologic risk factors for postoperative recurrence in CD have gained interest. Paneth cells are specialized cells in the crypts of the small bowel, and are linked to CD pathogenesis. Previous studies have identified abnormal Paneth cells as predictors of postoperative endoscopic recurrence. In **chapter 7**, ileocolonic resection specimen of CD patients were reviewed and assessed for markers of Paneth cell dysfunction, to assess the association with abnormal functioning Paneth cells and surgical recurrence.

Part III: Prevention

The third part of this thesis focusses on medical prophylaxis of postoperative recurrence. International guidelines advise to start postoperative prophylactic medication to prevent recurrence after ICR in high-risk patients with CD. **Chapter 8** describes a prospective observational multicenter study in which the outcome of a management algorithm incorporating clinical risk stratification is evaluated. Furthermore, the prognostic value of known clinical and histological risk factors is assessed.

Current guidelines recommend postoperative prophylaxis with anti-TNFα agents or thiopurines. **Chapter 9** describes a network meta-analysis of individual participant data of published RCTs, aiming to establish an absolute risk prediction and comparative efficacy of anti-TNFα vs thiopurines for the prevention of postoperative recurrence after ICR in patients with CD.

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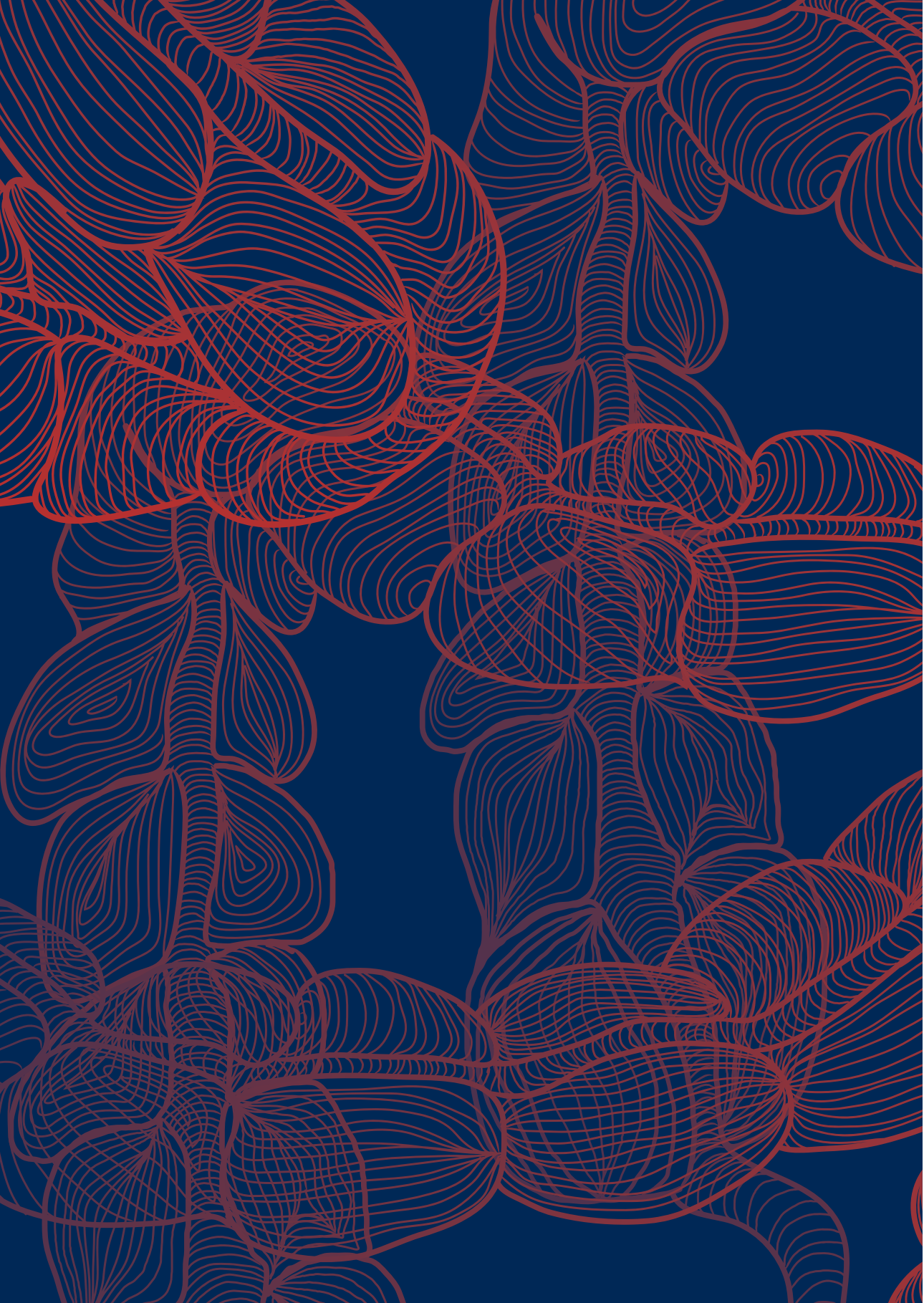
PART I

Epidemiology



CHAPTER 2

Decreasing trends in intestinal resection and re-resection in Crohn's disease: a nationwide cohort study

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on behalf of the Dutch Initiative on Crohn's and Colitis (ICC)

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Abstract

Objective

To assess time trends in intestinal resection and re-resection in Crohn's disease (CD) patients.

Summary of Background Data

CD treatment has changed considerably over the past decades. The effect of these advances on the necessity of intestinal resections and the risk of re-resection is unclear.

Methods

In this nationwide cohort study, adult CD patients with ileocolonic, small bowel, colon, or rectum resections between 1991 and 2015 were included. Data were retrieved from the Dutch nationwide network and registry of histopathology and cytopathology (PALGA). Time trends were analyzed with a broken stick model and Cox proportional hazard model with smoothing splines.

Results

The identified cohort comprised 8,172 CD patients (3,293/4,879 male/female) in whom 10,315 intestinal resections were performed. The annual intestinal resection rate decreased nonlinearly from 1.9/100,000 (1991) to 0.2/100,000 (2015). A significantly steeper decrease was observed before 1999 (slope -0.13) as compared to subsequent years (slope -0.03) ($p<0.001$). Analogous trends were observed for ileocolonic, small bowel and colon resections. Overall cumulative risk of re-resection was 10.8% at 5 years, 18.4% at 10 years and 28.2% at 20 years after intestinal resection. The hazard for intestinal re-resection showed a nonlinear decreasing trend, with HR 0.43 in 2000 and HR 0.28 in 2015 as compared to 1991.

Conclusions

Over the past 25 years, intestinal resection rate has decreased significantly for ileocolonic, small bowel, and colonic CD. In addition, current postoperative CD patients are at 75% lower risk of intestinal re-resection.

Background

Crohn's disease (CD) patients are at a high risk of intestinal resection. According to the available studies, the cumulative risk of intestinal surgery in CD is 50% after a disease duration of 10 years.[1] The need for intestinal resection in CD may be decreasing, as CD management has changed significantly over the past decades.[2–4] First, treatment goals have shifted from primarily symptom control to mucosal healing, which is associated with a better CD prognosis, characterized by long-term clinical and endoscopic remission as well as increased quality of life.[5,6] Second, widespread availability and early use of immunomodulatory and biological agents have changed treatment algorithms. The exposure to immunosuppressants as well as anti-tumor necrosis factor (TNF) has increased significantly over the past decades.[7] Third, strict monitoring to achieve the treatment goals has been introduced, with lower thresholds for endoscopy or radiologic imaging, and this strategy has made important leaps forward by implementation of noninvasive fecal calprotectin tests and therapeutic drug monitoring.[8] In addition to these changes in general CD management, the need for re-resection after first intestinal resection may be reduced after large trials have advocated specific strategies to prevent postoperative CD recurrence[9–11] and international guidelines focusing on the management of CD to prevent postoperative recurrence were deployed.[12,13]

The impact of these changed treatment paradigms on the frequency of intestinal surgery in CD and the risk of re-resection is uncertain. Available studies have shown conflicting results and have reported decreasing trends[14–16] as well as stable rates.[17–19] Important shortcomings of available data are the lack of details on the anatomic location of intestinal resection, and the relatively small size of the cohorts. Moreover, data from most recent years are required, as CD treatment strategies are continuously evolving. Data on the rate of necessity of re-resection would be highly valuable, as a decrease in surgical recurrence is a robust indicator of improved postoperative prognosis. In this study, we aimed to assess recent time trends in rates of intestinal resection as well as re-resection for CD in a nationwide cohort study in the Netherlands.

Methods

Data collection

All histopathology and cytopathology reports in the Netherlands are stored in the Dutch nationwide population-based pathology database (PALGA). Patients are pseudonymized with a unique code and all consecutive pathology reports are combined with standardized diagnostic codes to allow for anonymized follow-up per patient. Since 1991, this database has nationwide coverage.[20] Follow-up data were evaluated until December 2015.

All patients aged ≥18 years with a histological diagnosis of CD, as coded by a pathologist, and an intestinal resection between 1991 and 2015 were identified in the PALGA database. All ileocolonic resections, small bowel resections, colon resections, and rectum resections were identified from the database using specific diagnostic coding, registered by the pathologist when writing the pathology report **(Appendix, Supplementary data**) intestinal resections for malignancy were excluded through specific coding and hand-searching. Afterwards, duplicate (revision material) reports were excluded. For each patient, the following characteristics were available: sex, date of birth, date of pathology report, summary of pathology text, and diagnostic code. The date of death is not provided in PALGA, unless an autopsy had been performed. Therefore, censoring for death was derived from survival data from Statistics Netherlands (CBS).[21] For each patient, the imputed total follow-up time was based on life expectancy in the year of birth, assuming the survival of CD patients is similar to the general population.[22,23]

Statistical analysis

Statistical analyses were performed with IBM SPS Statistics version 22.0 (IBM Corp. Released 2013; IBM Corp, Armonk, NY) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages survival and splines.[24,25] Continuous data are presented as median and interquartile range (IQR). CD prevalence rates between 1991 and 2015 were estimated using prevalence in 2010, yearly CD incidence rates as reported by a recent population-based cohort study,[23] and the life expectancy given the patient's year of birth, under the assumption life expectancy in CD patients is similar to the general population.[22,23] Total population numbers and mortality rates in the Netherlands were available via Statistics Netherlands (CBS).[26] To investigate whether the assumed similar life expectancy of CD patients as compared to the general population has affected our results, a sensitivity analysis was performed using an elevated standardized mortality ratio of 1.38 in CD patients, as described by Bewtra et al.[27]

Time trends in intestinal resections

The annual number of resections per 5-year interval and corresponding patient characteristics were described and compared across intervals. Medians were compared using Mann-Whitney *U* tests.

Time trends in the number of intestinal resections corrected for CD prevalence (number of resections per 100,000 CD cases) were explored and modeled using linear regression with natural cubic splines (for all types of resection and per anatomic location). Visual inspection indicated that the curve could be sufficiently approximated by a piecewise linear model,[28] which facilitates a more straightforward interpretation. The piecewise linear model used 1 breakpoint and allowed different linear fits on either side. The position of the breakpoint was chosen to optimize the Bayesian information criterion (BIC) and the

BIC of the simplified model compared to that of the original model to confirm that the approximation was appropriate.

Intestinal re-resection

The cumulative incidence of re-resection (for all types of resections and per anatomic location), was assessed using Kaplan-Meier survival analysis and compared using log-rank test. Cox-regression analysis was performed to evaluate the association of re-resection with sex, age at first resection, year of first resection, and anatomic location of first resection. To investigate the shape of this association, in a second step, the effects of continuous covariates (age and year of first resection) were modeled using penalized splines (p-splines), which allow deviation from the standard assumption of linear effects. Nonlinearity was tested using Chi-squared goodness-of-fit tests.[29]

Results

Study population

The identified cohort comprised 8,172 CD patients (male 3,293 (40%); female 4,879 (60%)), with a median age of 38.0 years (27.0 – 51.0) at (first) intestinal resection, in whom 10,315 intestinal resections were performed between 1991 and 2015. According to anatomic location, the first identified intestinal resection was an ileocolonic resection in 3,186 / 8,172 patients (39%), small bowel resection in 2,551 (31%), colon resection in 2,262 (28%) and rectum resection in 173 (2%). **Table 1**

Table 1. Patient characteristics

			Total (N=8172)
Male sex		N (%)	3293 (40)
Age at intestinal resection (years)		Median (IQR)	38.0 (27.0 – 51.0)
Number of intestinal resections	**1**	N (%)	6658 (81)
	2		1160 (14)
	> 2		354 (5)
Anatomic location first intestinal resection	**Ileocolonic**	N (%)	3186 (39)
	Small bowel		2551 (31)
	Colon		2262 (28)
	Rectum		173 (2)

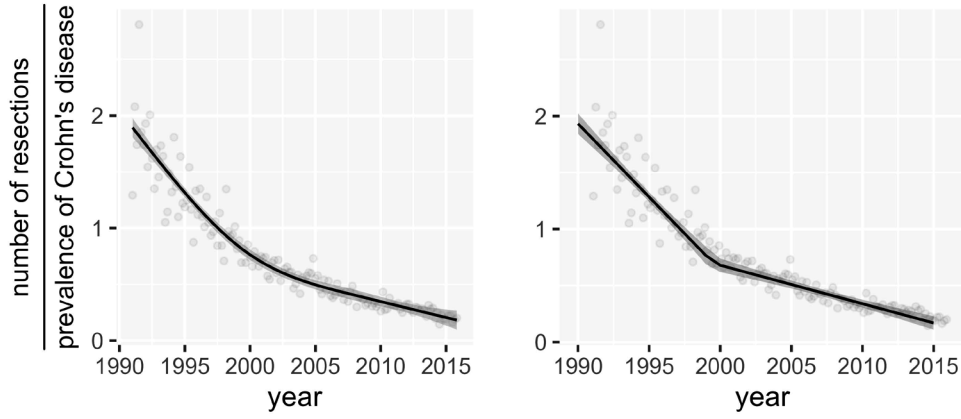
IQR: interquartile range

Time trends in intestinal resections

An increase in the mean absolute annual number of intestinal resections was observed during the study period, for all specific anatomic locations. Patients underwent intestinal resection at a significant younger median age during the period 1991-1995 (35.0 years [IQR 27.0 – 49.0]) and the period 1996-2000 (37.0 years [IQR 28.0 – 50.0]), as compared to subsequent time periods, p<0.001. No further significant increase in age at resection was observed after the year 2000. **Supplementary table 1, Supplementary data**

The total intestinal resection rate decreased nonlinearly during the study period from 1.9/100,000 in 1991 to 0.2/100,000 in 2015. **Figure 1A** The piecewise linear model used a breakpoint in 1999 with a slope of -0.13 (95% CI [-0.14, -0.11]) per year before 1999 and -0.03 (95% CI [-0.04, -0.03]) per year after 1999 (both p<0.001). **Figure 1B**

Figure 1. Intestinal resection rate in CD patients between 1991 and 2015 (A) its corresponding piecewise linear model (B) and corresponding 95% confidence intervals.

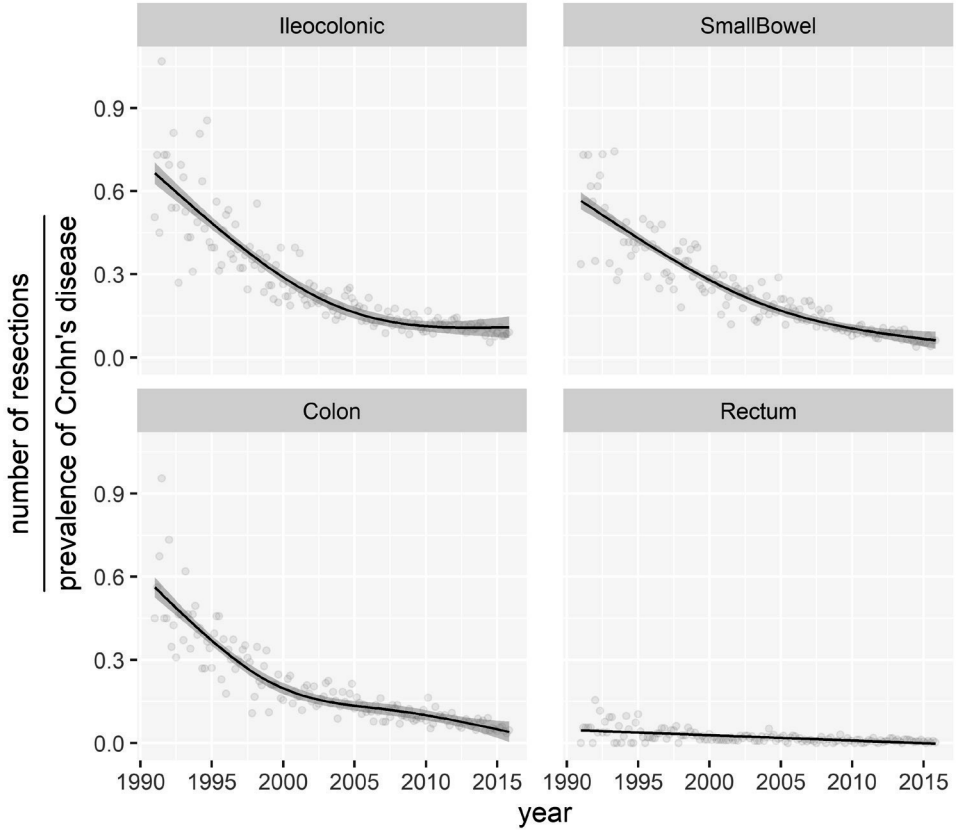


Prevalence of Crohn's disease: prevalence per 100,000 persons

Similar nonlinear decreasing trends were observed for all subgroups of intestinal resection. The overall decrease was most substantial for ileocolonic resections, from 0.7/100,000 in 1991 to 0.1/100,000 in 2015. Colon and small bowel resections decreased from 0.6/100,000 in 1991 to 0.05/100,000 in 2015 and 0.6/100,000 in 1991 to 0.07/100,000 in 2015, respectively. **Figure 2** Rectum resection rates decreased from 0.05/100,000 in 1991 to 0.001/100,000 in 2015. Piecewise linear models used the year 2000 as the breakpoint for ileocolonic resections and small bowel resections, with corresponding slopes before and after 2000 of -0.05 (95% CI [-0.05, -0.04]) and -0.01 (95% CI [-0.01, -0.01]), respectively, for ileocolonic and -0.03 (95% CI [-0.04, -0.03]) and -0.01 (95% CI [-0.02, -0.01]) for small bowel resections (all p<0.001). The year 1998 was found to be the breakpoint for colon resections, with a slope of -0.04 (95% CI [-0.05, -0.04]) before 1998 and -0.01 (95% CI [-0.01,

-0.01]) after 1998. Rectum resection models showed a linear decrease without the need for a breakpoint. Here the slope was -0.002 (95%CI [-0.002, -0.001]). **Supplementary figure 1, Supplementary data** All piecewise linear models approximated the smooth fit sufficiently well (difference in BIC < 5).

Figure 2. Intestinal resection rate in CD patients according to anatomic location: Ileocolonic, colon, small bowel, and rectum and corresponding 95% confidence interval.



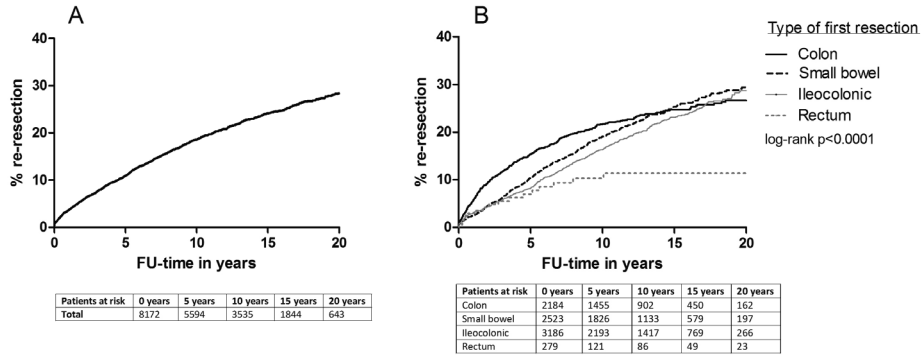
Prevalence of Crohn's disease: prevalence per 100,000 persons.

Intestinal re-resection

During a median follow-up of 9.4 years (4.4 – 15.3) after first resection, intestinal re-resection was performed in 1,547 / 8,172 (19%) patients and more than 2 intestinal resections were performed in 354 / 8,172 (5%) patients. The re-resection concerned a small bowel resection in 563 / 1,547 (36%) patients, ileocolonic resection in 482 (31%) patients, colon resection in 391 (26%) patients and rectum resection in 111 (7%) patients. **Supplementary table 2, Supplementary data**

The cumulative incidence of intestinal re-resection in the total cohort was 10.8%, 5 years after the first resection, and increased to 18.4%, 23.9% and 28.2% after 10, 15 and 20 years of follow-up, respectively. **Figure 3A** The cumulative incidence of intestinal re-resection after isolated colon resection was 15.4% at 5 years, 21.5% at 10 years, 24.7% at 15 years and 26.9% at 20 years after first intestinal resection. Intestinal re-resection rates for small bowel resection were 10.5%, 19.0%, 25.0% and 29.3% and for ileocolonic resection 8.0%, 16.2%, 23.1% and 28.7%, after 5, 10, 15 and 20 years. Intestinal re-resection rates after rectum resection were lower, 6.9% at 5 years increasing to 10.3%, 11.2% and 14.4% at 10, 15 and 20 years respectively, (log-rank p<0.001). **Figure 3B**

Figure 3. Cumulative risk of intestinal re-resection during follow-up for the total study population (A) and according to anatomic location of first resection (B).



Patients at risk	0 years	5 years	10 years	15 years	20 years
Total	8172	5594	3535	1844	643

Patients at risk	0 years	5 years	10 years	15 years	20 years
Colon	2184	1455	902	450	162
Small bowel	2523	1826	1133	579	197
Ileocolonic	3186	2193	1417	769	266
Rectum	279	121	86	49	23

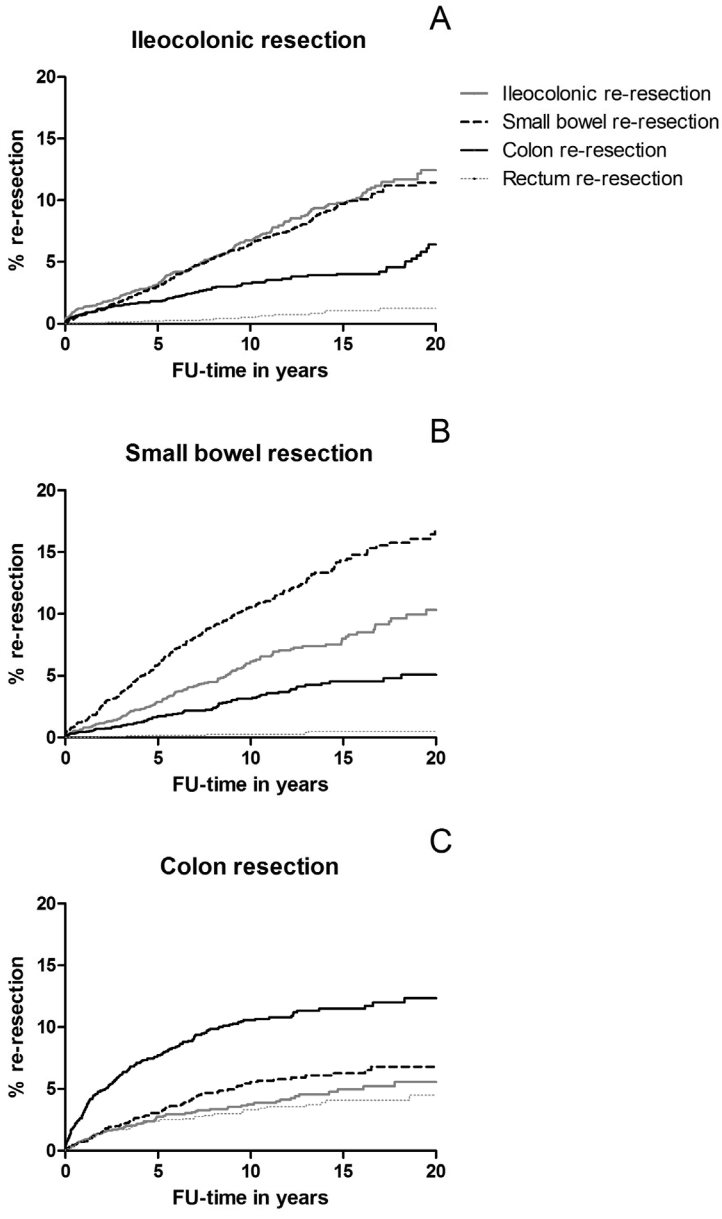
FU indicates follow-up

The risk of intestinal re-resection per anatomic location of first resection and re-resection is shown in **Figure 4A-C.** After ileocolonic resection, the cumulative risk of re-resection after 10 years was 6.7% for ileocolonic anastomosis, 6.4% for small bowel and 3.3% for colon. After small bowel resection, the risk of re-resection after 10 years was 10.5% for small bowel, 6.1% for ileocolon and 3.1% for colon. After a colonic resection, the risk of a re-resection after 10 years was 10.6% for colon, 3.8% for ileocolon and 5.6% for small bowel.

In multivariable Cox regression analysis, colon resections and small bowel resections had significantly higher hazards of re-resection as compared to ileocolonic resections, HR 1.38 (95% CI [1.21 - 1.56]) p<0.001 and HR 1.17 (95% CI [1.03 – 1.32]) p=0.015. Patients who had had a rectum resection had a lower hazard as compared to patients with ileocolonic resections, HR 0.61 (95% CI [0.39 – 0.96]) p=0.032. Older age at the moment of first resection was a significant protective factor for postoperative intestinal re-resection in multivariable analysis, HR 0.99 per year (95% CI [0.98 – 0.99]) p<0.001. Finally, patients undergoing the first resection during a later calendar year of follow-up were at significantly lower hazard of

re-resection, HR 0.94 per year (95% CI [0.93 – 0.95]) p<0.001, indicating a decreasing time trend in intestinal re-resection between 1991 and 2015. There was no evidence for an effect of gender. **Supplementary table 3, Supplementary data**

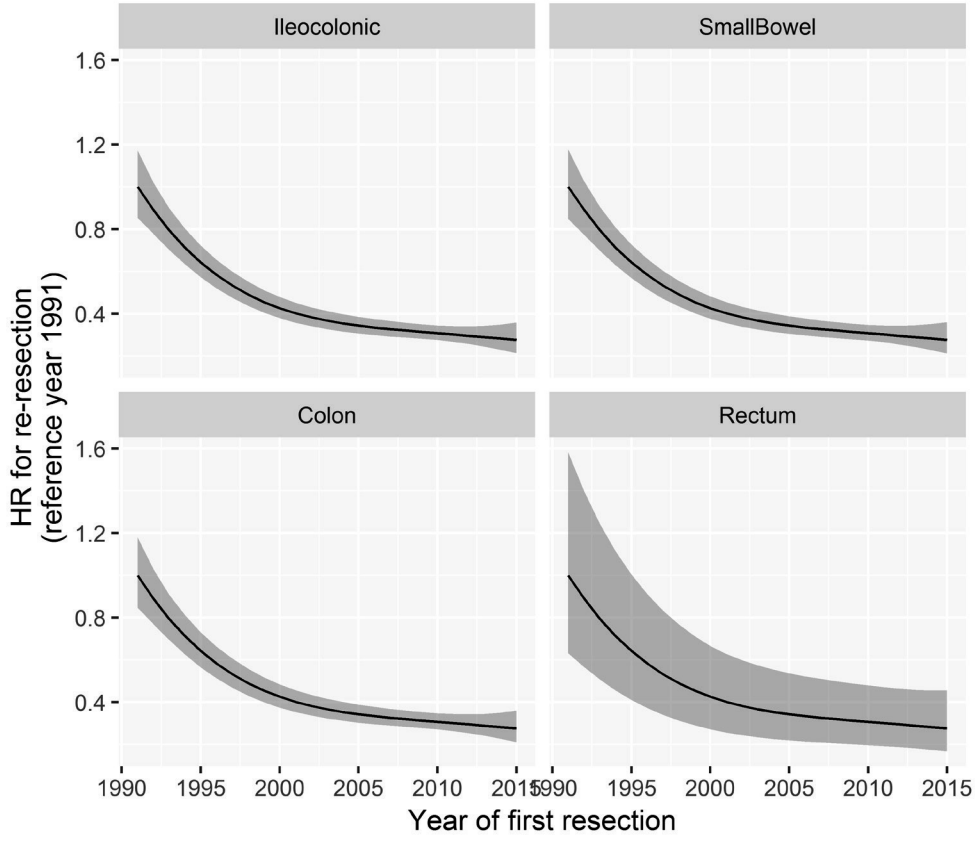
Figure 4. Cumulative risk of intestinal re-resection according to anatomic location of initial resection: ileocolonic (A), small bowel (B), and colon (C).



FU indicates follow-up.

Chi-squared tests for goodness-of-fit showed the effect of year of first resection was non-linear. There was no evidence of a non-linear effect of age at first resection. Visualization of the multivariable Cox model showed the steepest decline in HR for re-resection was observed during the first years of inclusion. **Figure 5** As compared to 1991, corresponding HRs decreased to 0.43 in 2000 (95% CI approx. [0.38 – 0.48] for ileocolon, small bowel and colon; [0.27 – 0.67] for rectum), and 0.28 in 2015 (95% CI approx. [0.21 – 0.36] for ileocolon, small bowel and colon; [0.17 – 0.46] for rectum).

Figure 5. Hazard ratio for intestinal re-resection over the past 25 years (reference year 1991) and corresponding 95% confidence interval. Age and sex are set to reference values (median age = 37; sex = male).



Prevalence of Crohn's disease: prevalence per 100,000 persons. HR indicates hazard ratio.

Sensitivity analyses under the assumption of an elevated standardized mortality ratio of 1.38 did not show any significant differences in intestinal resection and re-resection rates.

Discussion

The risk of intestinal resection in CD patients has decreased significantly over the past 25 years according to the long-term follow-up data in this nationwide cohort. A substantial decrease of intestinal resections in CD patients over the past decades was observed for all anatomic locations. Furthermore, a decreasing trend in the risk of intestinal re-resection was observed, with a 4 times lower hazard in 2015 as compared to 1991.

Epidemiological trends on the intestinal resection rate in CD patients have been investigated widely, as intestinal resection can be regarded as a surrogate marker of CD course and prognosis. However, previous studies have shown inconsistent results, and both decreasing and stable trends have been reported. These inconsistencies may be explained by inclusion of a relatively small number of patients (ie, less than 500), hampering reliable assessment of epidemiological trends.[15,16,18,19,30] In contrast to our observations, a stable annual intestinal resection rate of 3.4/100,000 persons was observed in a large cohort of 359,124 hospitalized CD patients from the US Nationwide Inpatient Sample (NIS).[17] The intestinal resection rate is lower in these USA data as compared to our cohort, which can probably be explained by not correcting for the substantial rise in CD prevalence and the relatively short study period. In line with our results, a large study of 4146 CD patients who underwent an intestinal resection reported a significant decrease in risk of surgery in 4 pre-defined cohorts according to year of diagnosis, between 1979 and 2011. This observation was associated with a significant increase in use of thiopurines and anti-TNFα.[31]

Although we observed a continuing decrease of intestinal resections after 2000, the most substantial decreasing trend in intestinal resection and in intestinal re-resection was observed between 1991 and 1999. Important changes in CD diagnosis as well as management may account for these observations. Over the past decades, earlier disease detection has contributed to a less complicated disease phenotype at diagnosis over the past decades.[7] A lower risk of resection shortly after diagnosis due to less severe complications at diagnosis is probably an important explanation for the observed decline in intestinal resections, especially for the period before 1999. In addition, the decline in intestinal resections is paralleled by significant changes in drug therapy, most importantly the introduction of thiopurines and anti-TNFα.[32–35] A changing phenotype attributable to widespread use of immunomodulators and anti-TNFα, with less progression toward stricturing and penetrating disease complications, may have contributed to the observed decline in intestinal resections, before 1999 as well as the continuing decline after 2000. However, whether drug therapy changes the natural course of CD is still a matter of debate.[7,30] Instead or in addition to changing the course of disease, the introduction of more therapeutic options in CD may be a contributing factor to postponement of intestinal resection, a hypothesis that is supported

by our observation of a significant younger median age at resection between 1991 and 1999, as compared to time periods after 2000.

Other factors that may be involved in the decline of intestinal resections are strict monitoring of inflammation with broader access to endoscopy, including video capsule endoscopy (VCE), and validation of (new) radiologic tools, for example, computed tomography (CT) and magnetic resonance imaging (MRI).[36,37] In addition, noninvasive monitoring with fecal calprotectin has been implemented widely in clinical practice.[8] Furthermore, a decrease in the number of active smokers may have contributed to the decline in intestinal resections and re-resections.[30]

In this study, we focused on intestinal resections for nonmalignancy indications in CD, and resections with neoplasia were excluded from analysis. It may be hypothesized that the observed decrease in nonmalignancy indications may induce a shift in indications from refractory CD and CD complications (eg, stenosis, penetrating disease) toward neoplasia, especially when surgery is postponed. However, this hypothesis is not substantiated by our data. Before exclusion from the main analysis, 266 resections (87% colon) with neoplasia (178 carcinoma and 97 dysplasia) were identified during 25 years study period. Although these low numbers do not allow for time trend analysis, these data indicate that neoplasia represent only a small proportion of the indications for intestinal resection in CD. With regard to the absolute risk of neoplasia in CD, this finding needs to be interpreted cautiously as the number of intestinal neoplasia may be underestimated, due to the possibility of endoscopic resection of colonic neoplasia and coding IBD instead of CD in the PALGA database.

We observed a marked decreasing trend in intestinal re-resection risk during the entire study period from 1991 to 2015. This finding may probably be due to improved and continuously evolving postoperative CD management. The risk of re-resection in our cohort is lower as compared to the results of a meta-analysis of 6 population-based studies with data inclusion from time periods varying from 1970 to 1979 to 1996 to 2007, which reported a re-resection risk of 24.2% after 5 years, and 35.0% after 10 years.[38] This difference can partly be explained by the inclusion of older and smaller cohorts in the meta-analysis.

The anatomic location of resection and subsequent re-resection was the same in the majority of patients in our study, most notably after a first colon or small bowel resection. This implies the CD location in the bowel is rather stable during the disease course, which is supported by evidence of a relatively stable Vienna classification in terms of disease localization.[39] Patients with a first colon resection were at highest hazard of intestinal re-resection, and the most frequently performed type of re-resection was a repeated colonic resection. Our data are in line with a previously reported high risk of re-resection after a segmental colon resection.[40–42] However, as segmental colonic resections have apparent

advantages, for example, a reduced risk of permanent stoma and a better reported quality of life,[43,44] a debate on the surgical management of Crohn's colitis is ongoing.

To the best of our knowledge, this is the largest study reporting time trends in intestinal resection and re-resections in CD. This study substantially adds to available literature by showing more recent trends and yearly resection rates for the specific anatomic locations, in a CD population with nationwide coverage and an assured detection of all intestinal resections and follow-up per patient. Despite these strengths, a few limitations need to be considered. First, we regarded the first available surgical excerpt in our database as the first resection. In a small number of patients, this might be a re-resection, if the first resection was performed before 1991. This might have led to an underestimation of the re-resection risk in our results. Second, a relatively high proportion of patients with small bowel resections was included. We assume that ileocecal resections may be coded as small bowel resections in a proportion of patients. However, as coding has not changed during the study period, we anticipate that this misclassification is stable over time and has not influenced the evaluation of time trends. As mentioned above, the possibility of coding IBD instead of CD in the PALGA database may have led to an underestimation of the total number of intestinal resections. Nevertheless, time trend analysis of large number of resections during long-term follow-up will not be affected by accidental miscoding. Third, resections might have been performed for an indication other than CD, such as diverticulitis in a CD patient. However, as the number of cases is probably very limited and resections for malignancy were excluded, the effect on the results is presumably negligible. Finally, the most important limitation of this study is the lack of data on other associated factors for intestinal resection in CD, such as disease duration, smoking status, disease behavior, CD medication use, length of the resected segment, and surgical techniques. These additional data would enable interpretation of the contributing factors of the decline in surgery rate in times of rapidly changing CD management strategies.

In conclusion, our study demonstrated a substantial decrease in ileocolonic, small bowel, and colon resections in CD patients over the past 25 years, with the most significant decrease before 1999. The risk of intestinal re-resection has shown a striking decline over the past decades, and current risk is approximately 4 times lower as compared to 1991.

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Supplementary data

Appendix

The nationwide network and registry of histology and cytopathology in the Netherlands (PALGA) thesaurus codes used for data acquisition

Crohn's disease	D62160
Ileocecal	T65500T67000
Small bowel	Retrieval term 24
Colon	T67___
Rectum	T68___
Resection	P11100, P11200, P11101
Adenocarcinoma	M814__
Metastasis, carcinoma	M801__
Revision material	P307__

Supplementary table 1. Number of intestinal resections, described as total number and mean annual number, and median age according to era in which the intestinal resection was performed.

N = 10315		**1991-1995**	**1996-2000**	**2001-2005**	**2006-2010**	**2011-2015**
Intestinal resection (total)	N (annual mean N)	1454 (291)	1991 (398)	2182 (436)	2274 (455)	2414 (483)
Age at intestinal resection (years)	Median (IQR)	35.0 (27.0 – 49.0)	37 (28.0 – 50.0)	39.0 (30.0 – 52.0)	39.0 (28.0 – 52.0)	40.0 (29.0 – 53.0)
Ileocolonic resection	N (annual mean N)	538 (107)	725 (145)	763 (153)	806 (161)	996 (199)
Small bowel resection		460 (92)	689 (138)	759 (152)	777 (155)	709 (142)
Colon resection		412 (82)	518 (104)	594 (119)	632 (126)	637 (127)
Rectum resection		44 (9)	59 (12)	66 (13)	59 (12)	72 (14)

IQR: interquartile range

Supplementary table 2. Number of performed intestinal re-resections per type of first and second resection.

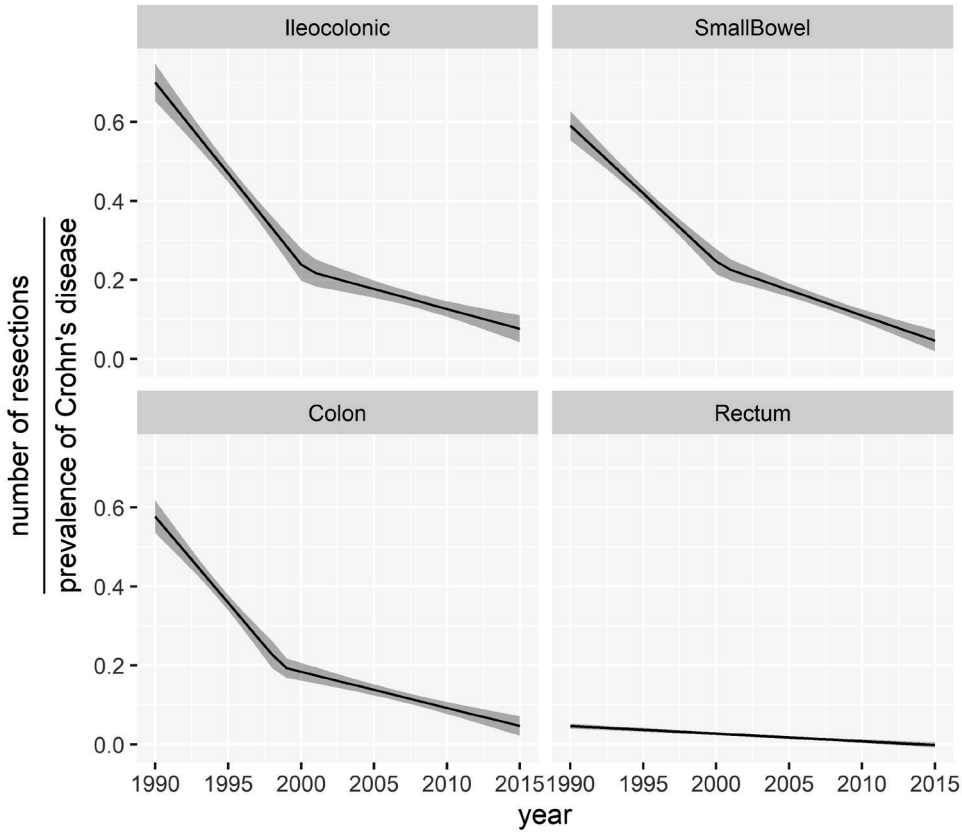
		Type of intestinal re-resection			
		Ileocolonic	Small bowel	Colon	Rectum
Type of first intestinal resection	Ileocolonic	237	204	107	19
	Small bowel	153	262	79	9
	Colon	90	91	200	77
	Rectum	2	6	5	6

Supplementary table 3. Multivariable Cox regression analysis identifying factors associated with re-resection

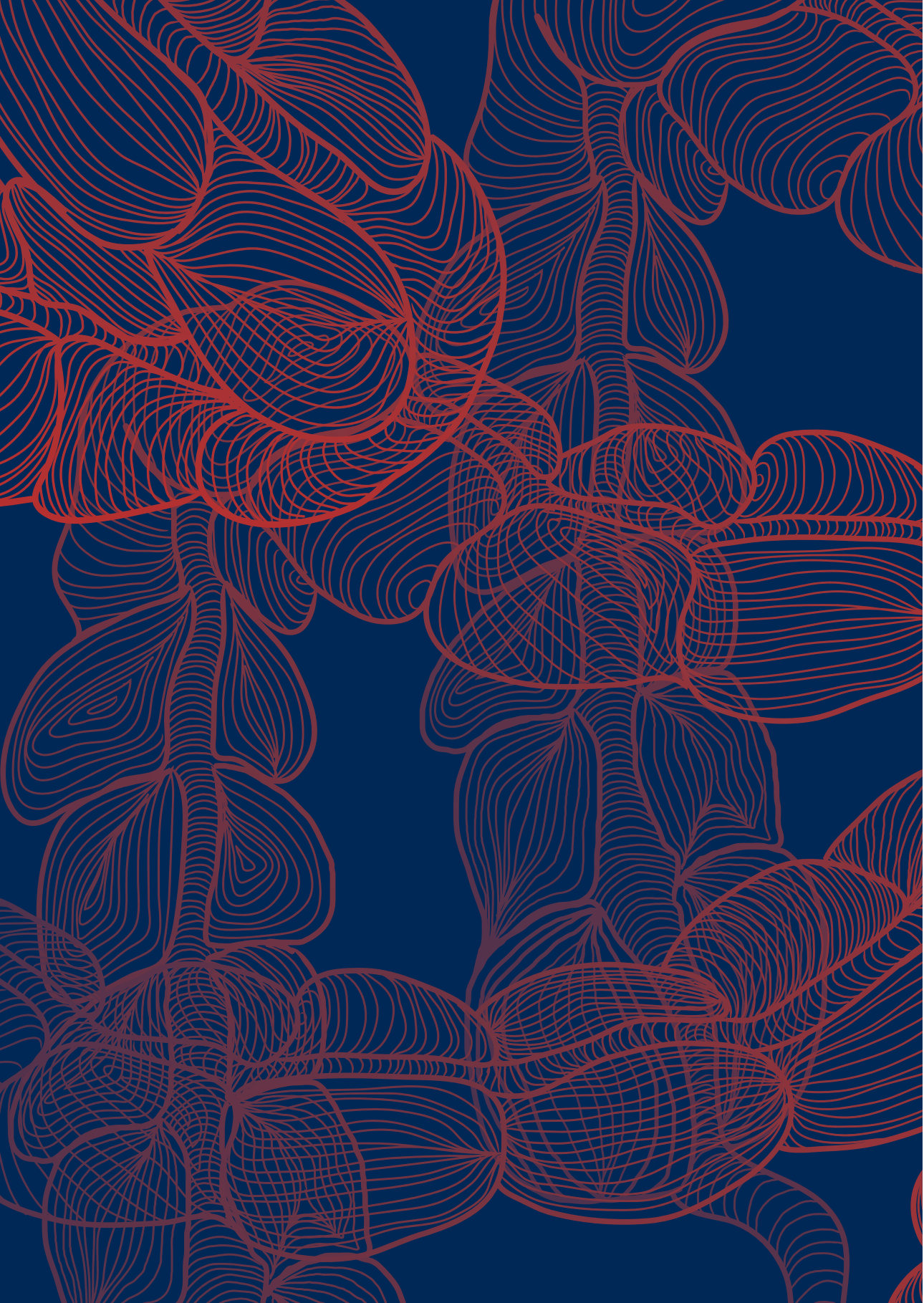
		Hazard Ratio (95% CI)	P-value
Male sex		0.97 (0.88 – 1.09)	0.678
Age at first resection (continuous)		0.99 (0.98 – 0.99)	< 0.001
Year of first resection (continuous)		0.94 (0.93 – 0.95)	< 0.001
Anatomic location of first resection	Ileocolonic	*1 (Ref)*	
	Small bowel	1.17 (1.03 – 1.32)	0.015
	Colon	1.38 (1.21 – 1.56)	< 0.001
	Rectum	0.61 (0.39 – 0.96)	0.032

CI: Confidence Interval

Supplementary figure 1. Piecewise linear analysis for decreasing trends in prevalence corrected intestinal resection rates, according to anatomic location of resection, and corresponding 95% confidence intervals.



Prevalence of Crohn's disease: prevalence per 100,000 persons



CHAPTER 3

Intestinal resection rates in Crohn's disease decline across two different epidemiological areas: a consistent observation not merely due to introduction of anti-TNFα

Evelien M.J. Beelen, C. Janneke van der Woude, Annemarie C. de Vries

Gut. 2020 September; 69(9): 1

With great interest we have read the manuscript written by Murthy et al, published in Gut in June 2019, on the influence of anti-tumour necrosis factor alpha (TNFα) therapy introduction on the rate of hospitalisation and intestinal resection rates in IBD.[1] Despite the difference in the source of data between both studies (Canada: health administrative data and the Netherlands: nationwide pathology database), a declining rate of intestinal resections in Crohn's disease has been confirmed in Canada, at equal rates as the decline that has been observed in the Netherlands.[2]

The authors used an advanced statistical method to analyse the impact of anti-TNFα introduction on (among other end points) the rate of intestinal resection. However, in our opinion, the hypothesised direct relationship between introduction of anti-TNFα and a decline in intestinal resection rate is vastly oversimplified for two important reasons. First, several other factors that have influenced both (early) diagnosis and management of Crohn's disease should be taken into account. Important changes over the past decades include improved access to endoscopy, less complications at diagnosis and development of strict and non-invasive monitoring strategies. In their original hypothesis, the authors also state the expectation that a similar linear decline during the years before introduction of infliximab would continue during the following years, in the absence of infliximab introduction. In our opinion, the observed decline before introduction of anti-TNFα rather confirms that other factors (as mentioned above) influence time trends of intestinal resection in Crohn's disease. Second, the effect of anti-TNFα introduction on the progression of Crohn's disease should preferably be measured on an individual patient level during long-term follow-up. In this publication, intestinal resection rates are only published on an epidemiological and economic level. Data that are essential to translate the epidemiological trends to clinical practice are the timing of anti-TNFα therapy after Crohn's disease diagnosis (ie, possibly only early medical intervention will impact the risk of intestinal resection), and the individual risk of intestinal re-resection (a marker of long-term prognosis after a 'reset' or 'new onset' Crohn's disease after resection).

The conclusion of the authors that the use of infliximab in Crohn's disease may be misguided as an explanation for the gradually declining rate of intestinal resections seems ingrained by the one factor-effect hypothesis described above. We would rather state more positively that among two different epidemiological areas, the intestinal resection rate in Crohn's disease is declining, probably as a marker of improved prognosis, attributed to the improvement of care to patients with Crohn's disease in various ways.

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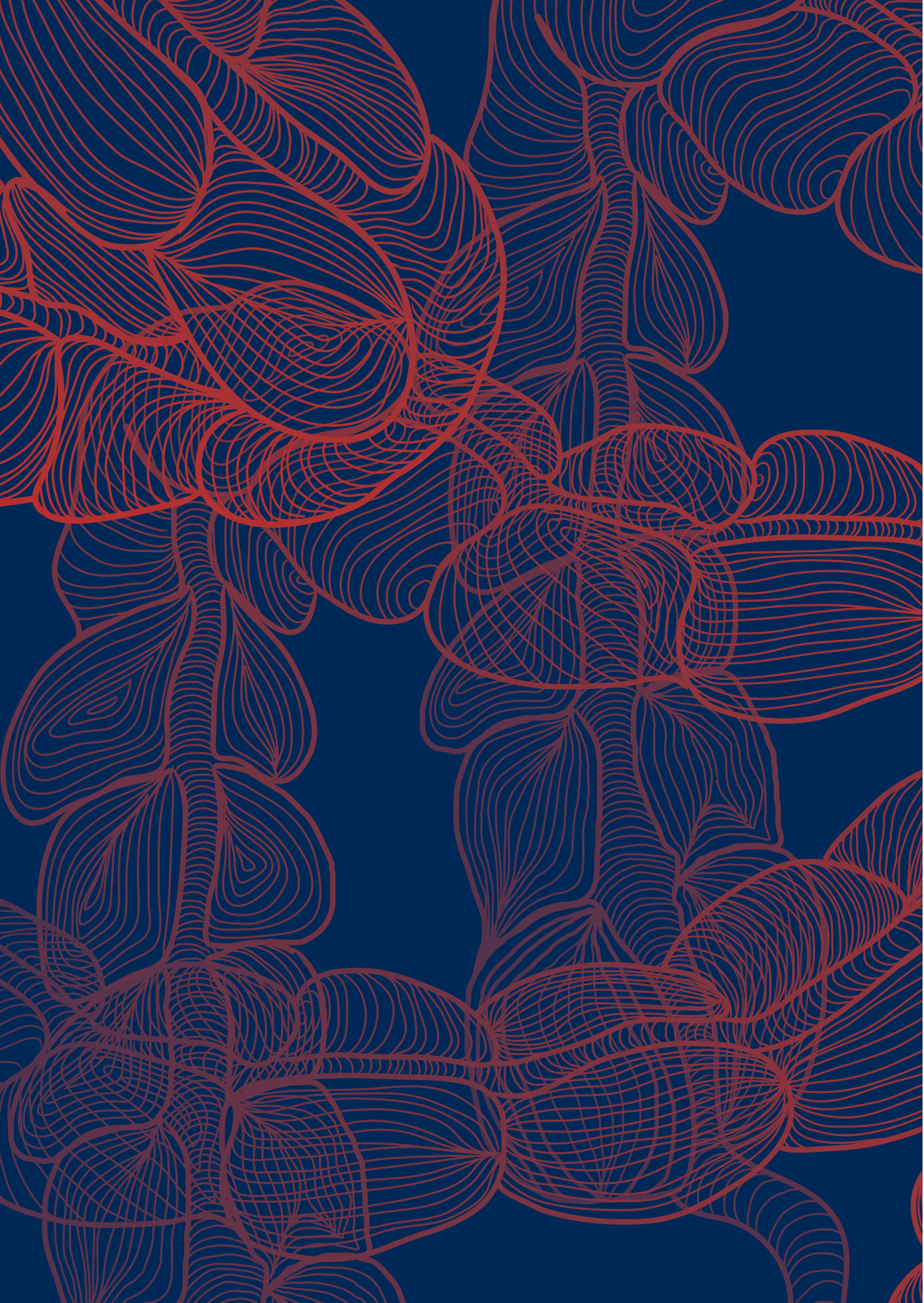

CHAPTER 4

Cholecystectomy risk in Crohn's disease patients after ileal resection: a long-term nationwide cohort study

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Abstract

Background

The risk of gallstone disease necessitating cholecystectomy after ileal resection (IR) in Crohn's disease (CD) patients is not well established. We studied the incidence, cumulative and relative risk of cholecystectomy after IR in CD patients, and associated risk factors.

Methods

CD patients with a first IR between 1991 and 2015 were identified in PALGA, a nationwide pathology database in the Netherlands. Details on subsequent cholecystectomy and IR were recorded. Yearly cholecystectomy rates from the general Dutch population were used as a reference.

Results

A cohort of 8302 (3466 (41.7%) males) CD patients after IR was identified. During the 11.9 (IQR 6.3–18.0) years median follow-up, the post-IR incidence rate of cholecystectomy was 5.2 (95% CI 3.5–6.4)/1000 persons/year. The cumulative incidence was 0.5% at 1 year, 2.4% at 5 years, 4.6% at 10 years, and 10.3% after 20 years. In multivariable analyses, female sex (HR 1.9, CI 1.5–2.3), a later calendar year of first IR ($HR_{/5\text{-year increase}}$, HR 1.27, CI 1.18–1.35), and ileal re-resection (time-dependent HR 1.37, CI 1.06–1.77) were associated with cholecystectomy. In the last decade, cholecystectomy rates increased and were higher in our postoperative CD population than in the general population (relative incidence ratio 3.13 (CI 2.29–4.28; $p < 0.0001$) in 2015).

Conclusions

Although higher in females, increasing in recent years, and higher than in the general population, the overall risk of cholecystectomy in CD patients following IR is low and routine prophylactic measures seem unwarranted.

Introduction

The annual incidence of newly diagnosed gallstones in Crohn's disease (CD) patients is twice as high as compared to the general population.[1] Ileal disease localization and previous ileal resection (IR) have both been identified as risk factors for developing gallstones in CD patients.[1,2] The underlying pathophysiology for the increased risk of developing gallstones in CD patients with ileal disease or after IR is not fully understood. A disturbance of the enterohepatic cycle of bilirubin, due to bile salt malabsorption in the ileum, may increase bilirubin secretion into the bile and thereby increase formation of gallstones. Alternative hypotheses are supersaturation of cholesterol in the bile due to reduced bile salt absorption or reduced motility and emptying of the gallbladder.[3-7]

Data on the prevalence of gallstones diagnosed with abdominal ultrasound in CD patients are variable, probably due to the inclusion of pooled populations of both symptomatic and asymptomatic CD patients. The reported prevalence ranges from respectively 10.4 to 38.5% in females and 9.4 to 25% in males and is clearly higher as compared to the reported prevalence in the asymptomatic general population, respectively 10.5% in females and 6.5% in males.[1,2,6,8-10] Available epidemiological data suggests an increased risk of symptomatic and/or complicated gallstone disease in CD patients.[1,2,6,10] A case-control study in 429 CD patients showed that the incidence rate of gallstones on abdominal ultrasound was 14.35/1000 persons/year compared to 7.48/1000 persons/year in matched hospital controls.[1] Additionally, this study suggested a significant proportion of patients with newly diagnosed gallstones would eventually require cholecystectomy for symptomatic gallstone disease ([9/41] 22%). A major limitation of this and other reports is the inclusion of small CD populations and lack of long-term follow-up data. In order to interpret the clinical relevance of the observed increased risk of gallstones in CD patients, studies assessing the risk of gallstone disease necessitating cholecystectomy are necessary. A high risk of cholecystectomy after IR justifies increased alertness in symptomatic CD patients and possibly even prophylactic measures at the time of IR, such as synchronous cholecystectomy. In this nationwide long-term follow-up study in the Netherlands, we aimed to assess the risk of—and identify risk factors for—cholecystectomy during long-term follow-up after IR in CD patients, including absolute annual and cumulative risk as well as the relative risk as compared to the general population.

Materials and methods

Histopathology database

In the Netherlands, all histopathology and cytopathology reports are collected in the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA). Since 1991, this database has a nationwide coverage.[11] Every individual patient within the database

is identified with a unique code that allows follow-up of all consequent pathology reports, regardless of the institute the patient is being treated. Every record in the database contains an excerpt combined with diagnostic codes given by the pathologist who assessed the tissue. The codes used are similar to the Systematized Nomenclature of Medicine (SNOMED) classification of the College of American Pathologists.[12] After a report has been coded, it is submitted online to the central database. The current study was based on data recorded in the PALGA database between 1991 and 2015. For each patient, the following characteristics were available: gender, date of birth, date of pathology review, summary text, and diagnostic code.

Patient selection

All patients aged ≥ 18 years with an IR (ileal or ileocolonic resection) and simultaneous histological diagnosis CD in the period from 1991 to 2015 were identified in PALGA. Corresponding details on subsequent IR and cholecystectomy were identified using PALGA pathology codes. **Appendix, Supplementary data.** Patients with a diagnosis of malignancy in the initial bowel resection specimen were excluded. Duplicate pathology reports (e.g., revision material) were excluded. Furthermore, patients with cholecystectomy prior to IR and patients of whom the first available excerpt in our database was an ileal re-resection were excluded. Patients with a cholecystectomy with gallbladder carcinoma, or gallbladder specimens resected in combination with other procedures such as hepatectomy or Whipple procedure, were excluded form analysis. Follow-up data were evaluated until December 2015. In addition, we obtained the yearly cholecystectomy rates for the general Dutch population aged ≥ 18 years from 1991 to 2015, using PALGA pathology codes, to create a reference study population **Appendix, Supplementary data.**

Statistical analysis

Statistical analyses were performed with IBM SPS Statistics version 22.0 (IBM Corp. Released 2013, IBM Corp, Armon, NY) and R version 3.4.0 (2017-4-21, R Foundation for Statistical Computing, Vienna, Austria) with the packages survival and splines.[13,14] Data are presented as median and interquartile range (IQR) for continuous variables. The PALGA database does not contain follow-up data on date of death unless an autopsy has been performed. Therefore, censoring for patient death was imputed from survival data of the general Dutch population from the Statistics Netherlands agency (CBS).[15] For each patient, the imputed follow-up was based on life expectancy in his or her year of birth, assuming the survival of CD patients is similar to that of the general population.[16,17] Interval between IR and cholecystectomy and cumulative incidence of cholecystectomies was evaluated using Kaplan-Meier survival analysis. Univariate and multivariate Cox-regression analysis was performed to identify factors associated with cholecystectomy.

The association of a second IR with a subsequent cholecystectomy was assessed by modeling the time until a second IR as a time-dependent covariate. Accompanying Kaplan-Meier

estimations were made using a clock-reset approach.[18] In this figure, a cumulative incidence curve was plotted for patients who only had one IR. Those who had a second resection during follow-up were censored and switched to a new cumulative incidence curve starting at time 0.

In addition, we assessed the yearly crude incidence rates of cholecystectomy in our CD population as well as in the general Dutch population. Cholecystectomy rates of the general Dutch population were obtained from PALGA. Data on total population numbers over calendar years were obtained from a Dutch registry (Statistics Netherlands, www.cbs.nl).[19] Joinpoint Regression Program, version 4.5.0.1, was used to examine significant changes in incidence over calendar time between 1991 and 2015.[20] Relative incidence ratios (relative risk) of cholecystectomy between our CD cohort and the general Dutch population were calculated at yearly intervals for the period 2001–2015 according to Altman.[21]

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Research Board of the corresponding center.

Results

Baseline cohort characteristics

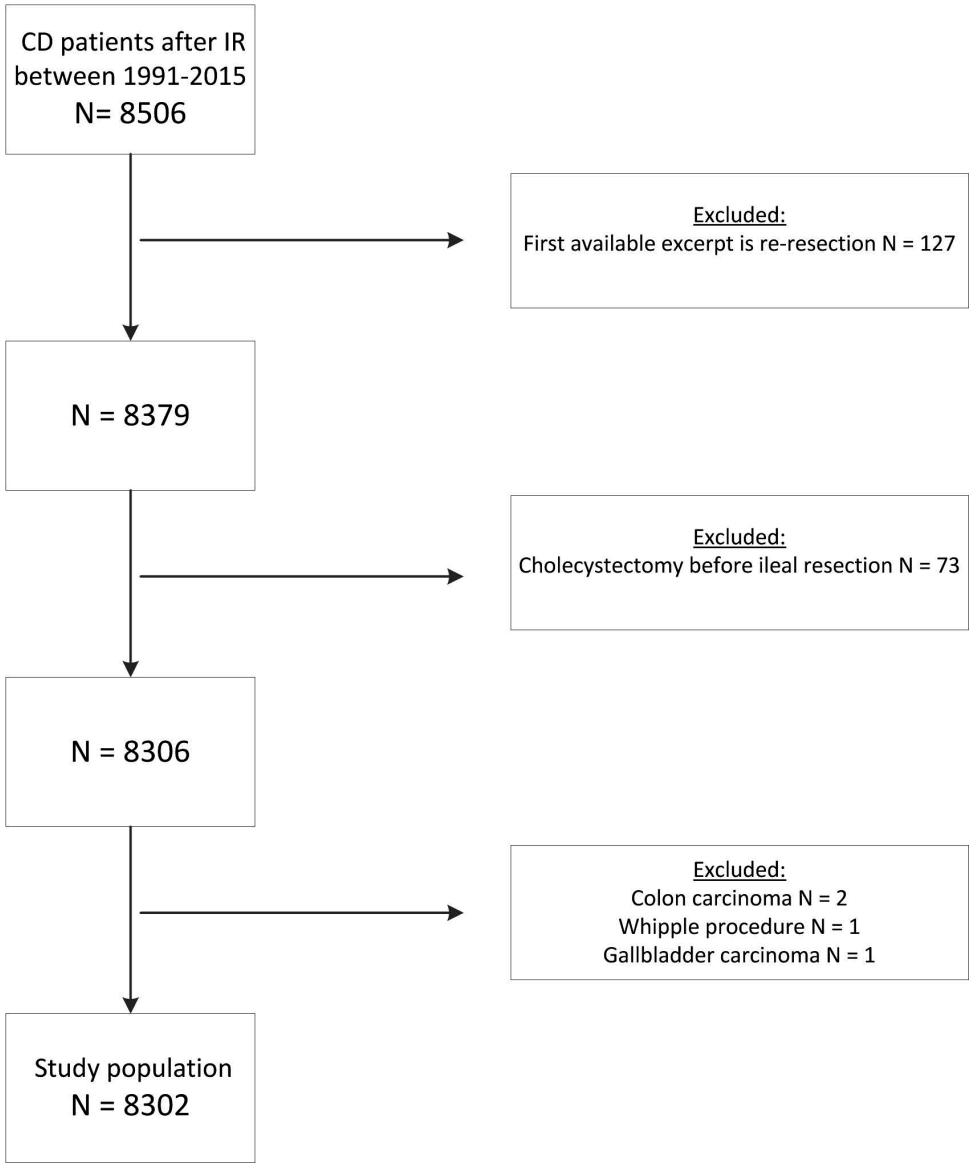
A cohort of 8506 adult CD patients who underwent an ileal resection between 1991 and 2015 was retrieved. After applying exclusion criteria, 8302 patients were included for further analysis. **Figure 1.** The majority of patients was female (4836; 58.3%) and the median (IQR) age at the first resection was 37.0 (27.0–51.0) years. **Table 1.** Median follow-up was 11.98 (IQR 6.31–18.05; range 0.0–25.0) years.

Table 1. Cohort characteristics. Data are presented as frequency (%) or median (IQR)

	Study population (N=8302)
Sex, male	3466 (41.7%)
Age at first IR	37.0 (22.0-51.0)
Calendar year of first resection	
1991-1995	1751 (21.1%)
1996-2000	1848 (22.3%)
2001-2005	1689 (20.3%)
2006-2010	1543 (18.6%)
2011-2015	1471 (17.7%)
Number of IR	1062 (12.8%)
1 resection	7240 (87.2%)
2 resections	854 (10.3%)
>2 resections	207 (2.5%)

IR, ileal resection

Figure 1. Flowchart of inclusion



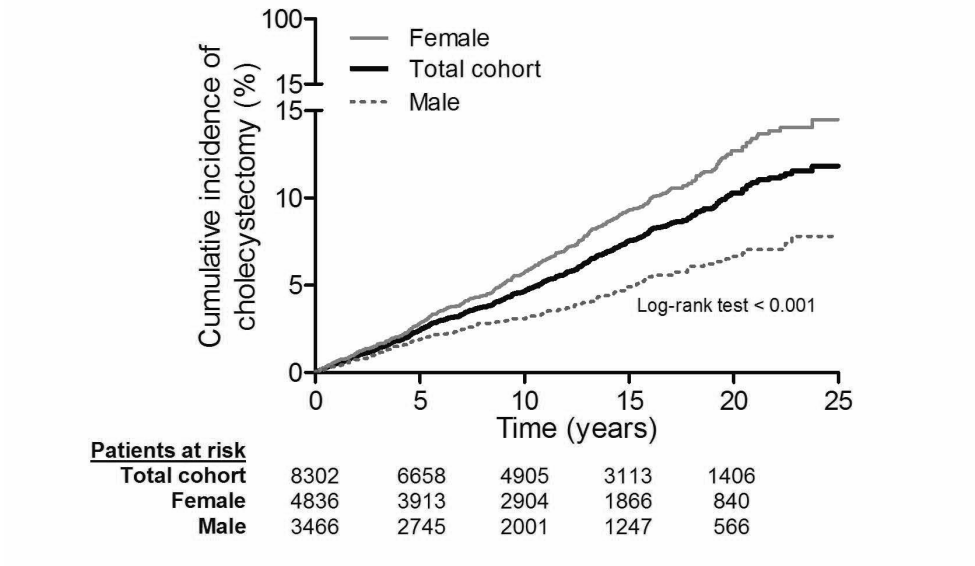
CD, Crohn's disease; IR, ileal resection.

Cumulative incidence of cholecystectomy

At the end of the 25-year follow-up period, a total of 523 (6.3%) patients had undergone a cholecystectomy: 143 males (1.7% of total population and 4.5% of male study population) and 380 females (4.6% of total population and 7.9% of female study population). The median (IQR) age at cholecystectomy was 45.65 (37.36–56.62) years. The incidence rates of

cholecystectomy at 1, 5, 10, and 20 years of follow-up were 0.5%, 2.4%, 4.6%, and 10.3%, respectively. **Figure 2.** Female CD patients had higher incidence rates of cholecystectomy than male patients: 0.6% vs. 0.3%, 2.8% vs. 1.9%, 5.7% vs. 3.1%, and 12.7% vs. 6.7%, at 1, 5, 10, and 20 years, respectively. **Figure 2.**

Figure 2. Cholecystectomy risk after ileal resection. Kaplan-Meier estimates of the occurrence of cholecystectomy in the total cohort stratified according to gender. Females had a significantly higher probability of cholecystectomy than males (log-rank test < 0.001 and HR 1.84 [95% CI 1.52–2.23; p < 0.001])



Factors associated with cholecystectomy

In univariable analysis, female patients had a significantly higher probability of cholecystectomy than male patients (HR 1.84 (95% confidence interval [CI] 1.52–2.23); $p < 0.001$; **Figure 2**). Furthermore, a later calendar year of the first IR was associated with an increased probability of cholecystectomy ($HR_{/5\text{-year increase}}$ 1.25; CI 1.16–1.34; **Figure 3**). Finally, ileal re-resection during follow-up was associated with a slightly increased probability of cholecystectomy (time-dependent HR 1.30; CI 1.01–1.68; $p = 0.045$; **Figure 4**). All these variables remained significantly associated with a cholecystectomy in multivariable analysis. **Table 2.**

Figure 3. Hazard ratio of cholecystectomy over calendar year of first ileal resection. Hazard ratio (solid line) and corresponding 95% confidence interval (dashed lines) for the association between calendar year of first IR and cholecystectomy. A later calendar year of the first IR was associated with an increasing hazard for cholecystectomy.

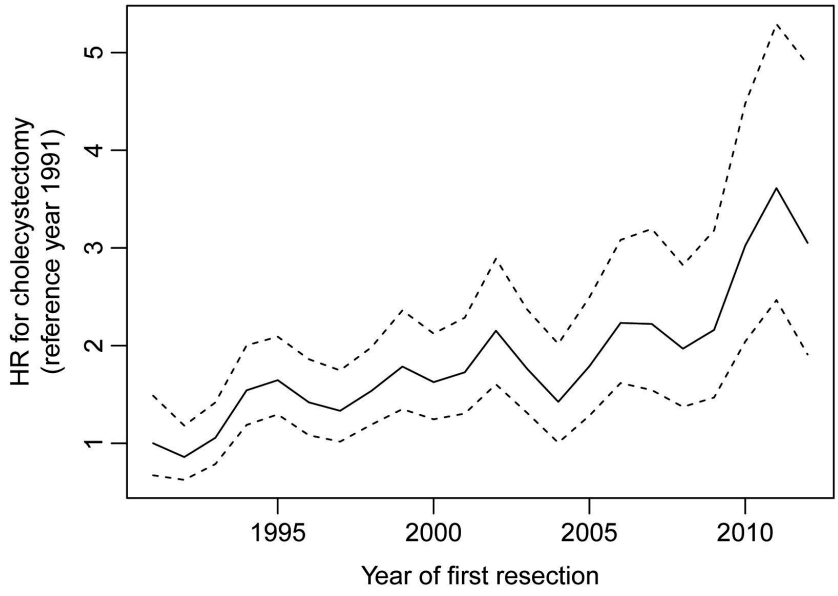
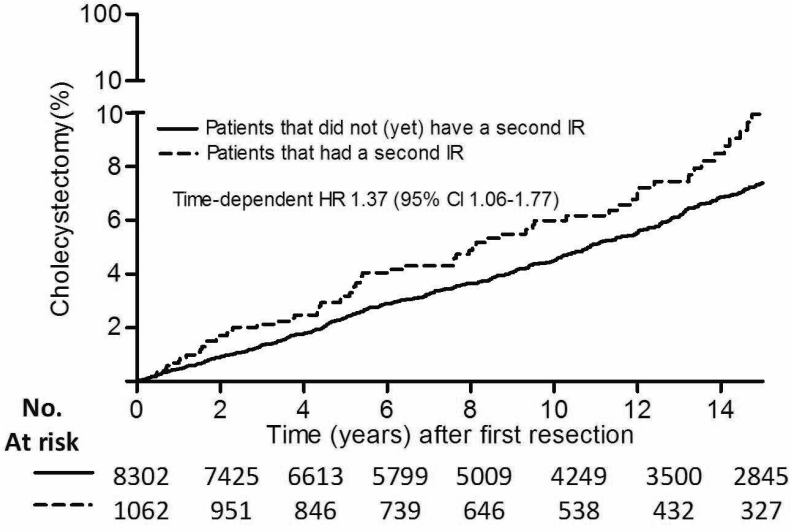


Figure 4. Cumulative incidence of cholecystectomy in a clock-reset approach: patients who only underwent one IR during their follow-up are in the solid line. Patients who underwent a second IR are represented in the solid line until they have a second IR. They are then censored and switched to a new survival curve (dotted line), which is then reset as time 0 for further follow-up. Patients with an ileal re-resection during follow-up had an increased probability of a cholecystectomy during their further follow-up.



IR, ileal resection

Table 2. Covariates associated with cholecystectomy

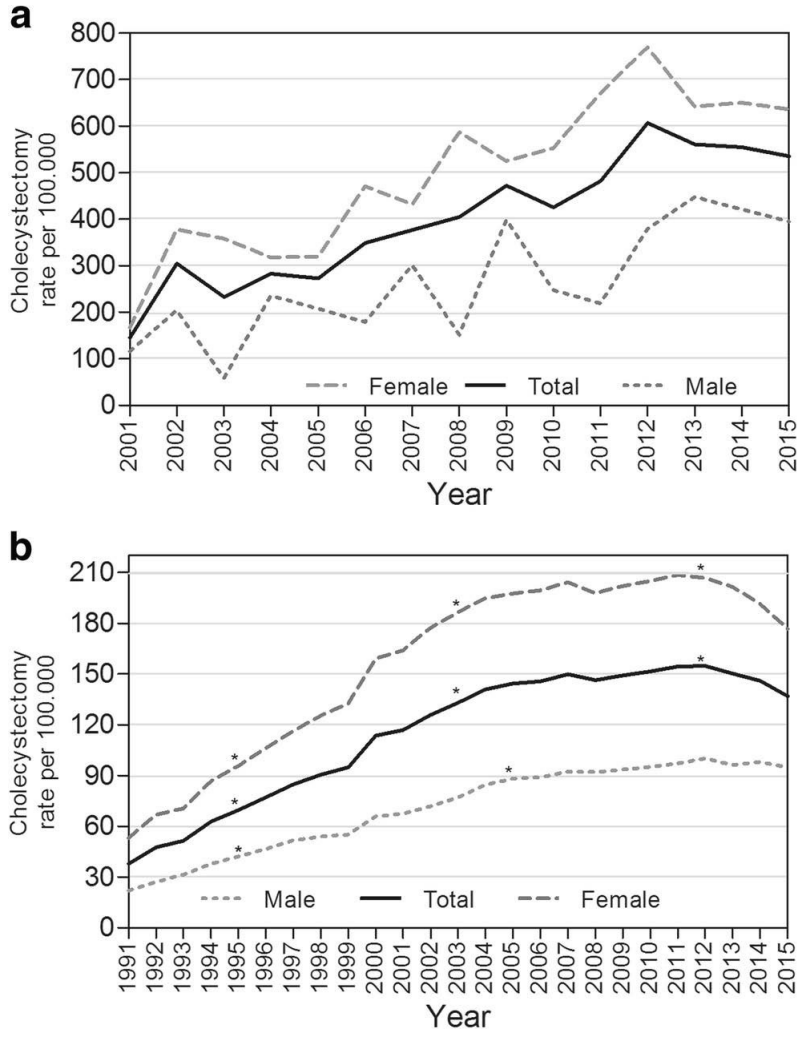
	Univariable analyses			Multivariable analyses		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
Female sex	1.839	1.517-2.229	<0.001	1.856	1.532-2.250	<0.001
Age at first resection	1.000	0.994-1.005	0.920			
Year of first IR, *per 5 years*	1.252	1.164-1.341	<0.001	1.265	1.177-1.350	<0.001
Ileal re-resection during FU[a]	1.299	1.006-1.678	0.045	1.369	1.059-1.769	0.016

[a] These hazard ratios were obtained by considering re-resection as a time-dependent covariate in univariable and multivariable analyses.
HR, hazard ratio; CI, confidence interval; IR, Ileal resection; FU, Follow-up

Yearly cholecystectomy rates in CD patients and the general population

During the median follow-up of 12 years, the incidence rate of cholecystectomy in our CD cohort was 5.2 (95% CI 3.5–6.4)/1000 persons/year. Females had a significantly higher rate than males (6.4 [95% CI 4.7–5.6] vs. 3.5 [95% CI 2.9–4.1]/1000 persons/year; $p < 0.0001$). Absolute cholecystectomy rates per calendar year were higher in our postoperative CD population **(Figure 5A)** than in the general Dutch population **(Figure 5B)** between 1991 and 2015. Over the last decade, the relative incidence ratio for our postoperative CD cohort, compared to the general population, varied between 1.28 (95% CI 1.28–2.81; $p = 0.001$) in 2002 and 3.13 (95% CI 2.29–4.28; $p < 0.0001$) in 2015. For males, these ratios were 2.16 (95% CI 1.028–4.52; $p = 0.042$) and 3.25 (95% CI 1.85–5.72; $p < 0.0001$) and for females 1.68 (95% CI 1.06–2.67; $p = 0.027$) and 2.90 (1.99–4.22; $p < 0.0001$), respectively. **Supplementary table 1, Supplementary data**. In accordance with the observed increase in the probability of cholecystectomy after IR in our CD population over calendar time, there was an increase in the crude incidence rates of cholecystectomies within the study population **(Figure 5A)**, which was also observed in the general Dutch population with a significant increase over calendar time from 48/100,000 in 1991 to 185/100,000 in 2006, and remained relatively stable with a minimal decline after 2012 **(Figure 5B).**

Figure 5. A Incidence rates of cholecystectomy per calendar year in CD patients. Crude incidence rates of cholecystectomy increased in our postoperative CD population from 2001 to 2015. Cholecystectomy rates between 1991 and 2001 are not presented in this figure because these initial years may not be representative as CD patients who underwent IR before 1991 are not included as background population. B Incidence rates of cholecystectomy in the general Dutch population per calendar year. Crude incidence rates of cholecystectomy increase over calendar year in the general Dutch population in males and females.



The asterisk indicates joint points where the annual percentage change (APC) is significantly different from 0 at the alpha = 0.05 level, indicating a significant trend.

Discussion

It has been well established that CD patients are at an increased risk of gallstone development, especially those with ileal involvement. The clinical relevance of this observed increase has however remained unclear. This large nationwide long-term follow-up study is the first to assess the risk of gallstone disease necessitating an intervention following IR, namely cholecystectomy. Our results show that, although over the past years the incidence of cholecystectomy in post-IR CD patients has increased and is currently higher than that in the general population, the annual incidence of cholecystectomy after IR is low. With thorough analyses, we were able to identify patients more likely to require cholecystectomy following IR. Female patients, those undergoing ileal re-resection, and patients with a later calendar year of first IR have an increased probability of cholecystectomy.

The observed incidence rate of cholecystectomy in our CD population after IR of 5.2/1000 persons/year is evidently lower than the reported incidence rate of gallstones found by ultrasound examination in CD patients in general. A large case-control study in 429 CD patients reported an incidence rate of gallstones on abdominal ultrasound of 14.35/1000 persons/year, which was significantly higher than that in matched controls (7.75/1000 persons/year, $p = 0.012$).[1] Additionally, it was shown that in a subgroup of CD patients with newly developed gallstones, about 22% of the patients (9/41) eventually required cholecystectomy for symptomatic stones. Our nationwide study substantially adds to these data by describing the clinical consequences of gallstones in a large long-term follow-up cohort of CD patients. Our study shows that in a potentially high-risk population for gallstone disease, only a minority of patients of approximately 10.5% during 20 years will eventually require a cholecystectomy.

The observed cumulative incidence of cholecystectomy of 4.6% within 15 years of follow-up in our study is evidently higher than that observed in the general population. A recent large population-based cohort study of over 65,000 individuals found a cumulative incidence of cholecystectomy for gallstone disease of 1.8% within 15 years of follow-up.[22] To date, the only published study on gallstone disease necessitating cholecystectomy in CD patients was a case-control study including 134 CD patients with ileitis.[10] This study demonstrated that the incidence of cholecystectomy was not significantly different from an age- and sex-matched control group. The nationwide data in the current study significantly adds to previous reports by quantifying the rate of cholecystectomy in absolute and relative risk, annual cholecystectomy risk, and cumulative cholecystectomy risk during long-term follow-up.

Female sex is an important risk factor for cholecystectomy after IR in our study. This finding is in agreement with data from the general population, in which female sex has been

identified as an important risk factor for gallstone development.[9,23] Especially women in fertile years are more likely to form gallstones as compared to men. This difference narrows after menopause.[24,25] However, previous data on the prevalence of gallstones in CD patients indicate there are no gender differences. A study in 251 CD patients showed no gender differences in the prevalence of gallstones (27% in females vs. 29% in males).[2] In accord, a more recent study in 330 CD patients reported similar results with a prevalence of 25% in females vs. 25% in males as found by ultrasound examination.[6] A possible explanation for the observed difference in our cohort may be the long-term follow-up and the larger number of included CD patients. Alternatively, the difference may be explained by our cohort's relatively young median age of 37 years.

In line with expectations, ileal re-resection was associated with cholecystectomy. Previous studies have shown that the prevalence of gallstones is associated with the number of bowel resections and is significantly increased in patients in whom more than 10 cm of the ileum was resected.[2,26] In the current study, we assessed re-resection as a surrogate for the length of intestine removed by surgery and/or CD severity, and this was associated with an increased risk of cholecystectomy.

To our knowledge, this is the first study to report on an increase in gallstone disease necessitating cholecystectomy after IR in CD patients over calendar time. Our findings may well reflect the global trend of increasing gallstone prevalence observed in necroptic27 and ultrasound studies.[24,28] In addition, cholecystectomy rates have increased, especially in the first decade after 1990.[29-31] This increase may be attributed to the introduction of laparoscopic cholecystectomy in 1990, which may have lowered the threshold for a surgical procedure in cases of uncomplicated gallstones.[32,33] Still, the cholecystectomy rates may vary greatly between different countries. A recent nationwide study from Sweden, which assessed a total of 130,800 laparoscopic and 47,641 open cholecystectomies performed between 1998 and 2013, showed the annual rates of cholecystectomies remained stable.[34] In contrast, our data covering all cholecystectomies performed within the Netherlands between 1991 and 2015 indicates annual rates have increased between 1991 and 2007 and remained relatively stable with a minimal decline after 2012. This corresponds with the observed increase in probability of cholecystectomy after IR in our study population.

One of the strengths of our study is the selection of a large nationwide cohort with long-term follow-up data, with stringent inclusion criteria of a histology-proven CD and the use of the general Dutch population as a reference population. These data allowed a thorough assessment of gallstone disease necessitating cholecystectomy including risk factors, absolute, relative, and cumulative risk. In addition, due to the nationwide coverage of PALGA, there was a long-term follow-up for each individual patient after IR and full-scale cholecystectomy detection. However, some limitations need to be considered. Firstly, our

inclusion criteria for a biopsy-proven CD (SNOMED D62160) might have been too stringent as some pathology reports only include SNOMED codes for ulcer, granuloma, or inflammation. Secondly, the PALGA database provides limited data on patient characteristics, making further subgroup analysis impossible. No data on initial diagnosis of CD and thus duration and/or severity of disease, length of the resected segment, ileal involvement earlier in the disease course, or other known risk factors (e.g., BMI, bariatric surgery) are provided. It would be highly interesting to assess these factors in such a large cohort. In addition, the PALGA database does not contain a date of CD diagnosis, thereby limiting the possibilities for time-to-event and risk factor analysis in a cohort of CD patients without IR. Further studies could focus on the comparison of the risk of cholecystectomy in CD patients without IR and those with IR. This would provide further evidence for the hypothesized role of IR in the development of gallstones in CD patients. Finally, data on the indication of cholecystectomy are lacking. Cholecystectomy rates in CD patients might be higher due to frequent contact with health care professionals and consequently a lower threshold for performing an abdominal ultrasound and a higher diagnosis rate of incidental gallstones. Furthermore, cholecystectomy may have been performed for indications other than complications of chole(cysto)lithiasis, e.g., polyp, tumor-like lesions, acalculous cholecystitis, and unexplained abdominal pain. However, in general, only a small proportion of patients undergo cholecystectomy for these indications.[34]

In conclusion, this large nationwide study shows that annual incidence of cholecystectomy in CD patients after IR is 0.5% and increases almost linearly during follow-up to 10.5% after 20 years. Female sex, re-resection, and a later year of IR are associated with cholecystectomy. The incidence of cholecystectomy after IR in CD patients is currently three times higher than that in the general population. Nonetheless, overall, the risk of cholecystectomy is low. While this risk may justify increased alertness of gallstone disease and a lower threshold for abdominal ultrasound in symptomatic CD patients following ileal resection, it does not seem to warrant prophylactic synchronous cholecystectomy during IR in all CD patients.

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Supplementary data

Appendix

PALGA diagnosis codes used in the analysis of our CD cohort

Crohn's disease: D62160

Ileum or ileocecal: T65200, T65500T67000, T65500, M81406

Resection: P11100, P11200, P11101

Gallbladder: T57000

Adenocarcinoma: M81403

Metastasis, adenocarcinoma: M81406

Metastasis, carcinoma: M80106

Intramucosal carcinoma: M80105

PALGA codes used to extract cholecystectomy rates in general Dutch population

Cholecystectomy: T57000111000

Gallbladder and excision: T57___ AND *54*

Supplementary table 1. Relative incidence ratios between Crohn's disease patients and the general Dutch population between 2001 and 2015.

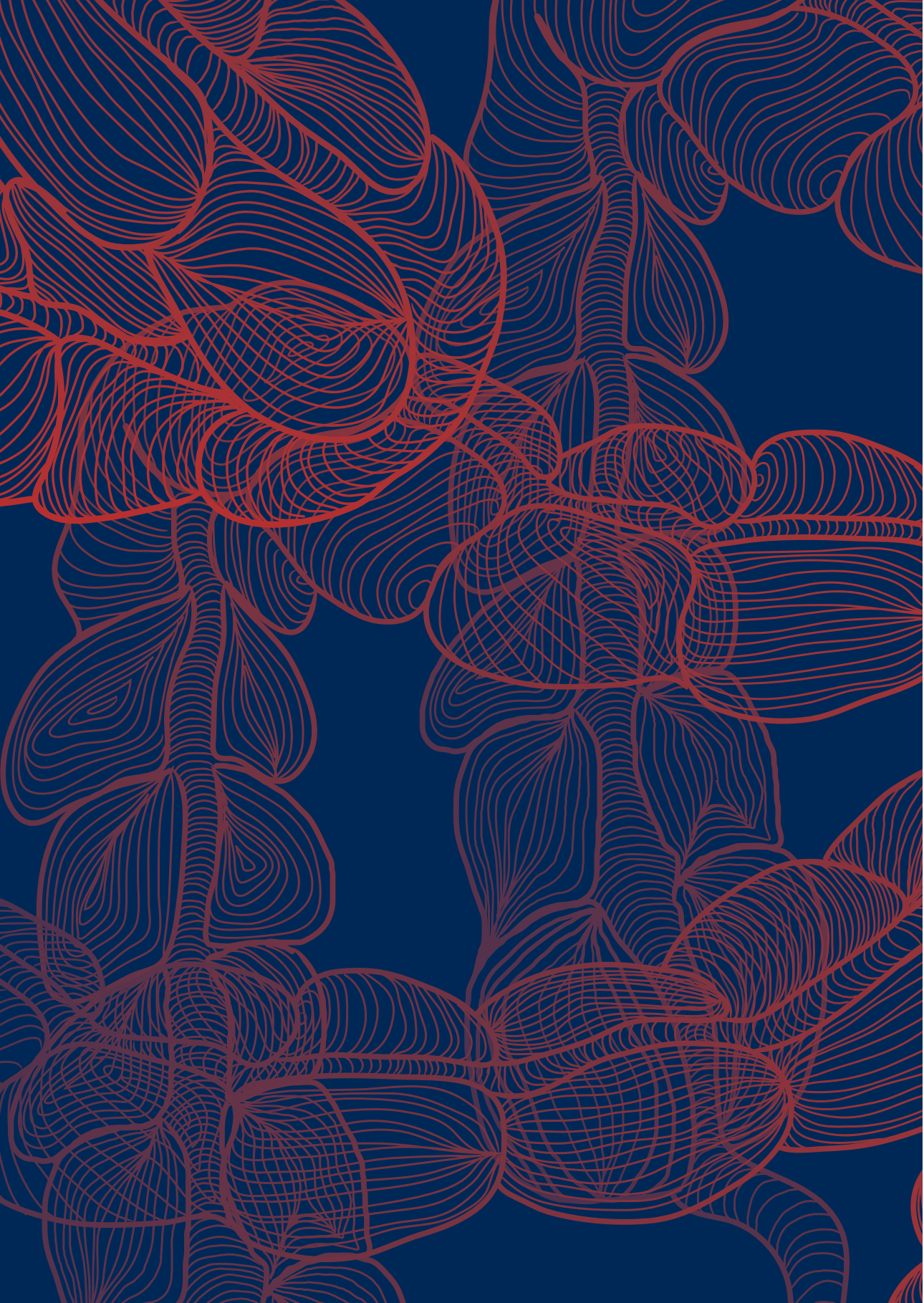
Calendar	Total cohort			Female			Male		
Year[a]	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
2001	0.98	0.55-1.72	0.9359	0.81	0.40-1.61	0.5419	1.31	0.49-3.49	0.5903
2002	1.90	1.28-2.81	0.0014	1.68	1.06-2.67	0.0270	2.16	1.03-4.52	0.0420
2003	1.37	0.87-2.15	0.1707	1.52	0.94-2.44	0.0846	0.58	0.14-2.31	0.7790
2004	1.57	1.05-2.37	0.0293	1.29	0.78-2.14	0.3217	2.12	1.06-4.24	0.0335
2005	1.48	0.98-2.25	0.0651	1.28	0.77-2.12	0.3376	1.79	0.85-3.75	0.1235
2006	1.88	1.30-2.73	0.0008	1.87	1.23-2.84	0.0032	1.54	0.69-3.42	0.2923
2007	1.98	1.38-2.83	<0.0001	1.68	1.09-2.60	0.0200	2.48	1.34-4.61	0.0040
2008	2.18	1.54-3.09	<0.0001	2.36	1.62-3.44	<0.0001	1.26	0.52-3.03	0.5180
2009	2.50	1.81-3.45	<0.0001	2.08	1.39-3.10	<0.0001	3.27	1.90-5.62	<0.0001
2010	2.23	1.58-3.13	<0.0001	2.16	1.46-3.19	<0.0001	2.00	1.00-4.00	0.0494
2011	2.49	1.80-3.43	<0.0001	2.58	1.81-3.69	<0.0001	1.74	0.83-3.65	0.1421
2012	3.12	2.34-4.16	<0.0001	3.00	2.14-4.19	<0.0001	2.93	1.66-5.15	0.0002
2013	2.98	2.21-4.03	<0.0001	2.57	1.78-3.72	<0.0001	3.61	2.14-6.09	<0.0001
2014	3.04	2.24-4.13	<0.0001	2.75	1.90-3.97	<0.0001	3.35	1.94-5.76	<0.0001
2015	3.13	2.29-4.28	<0.0001	2.90	1.99-4.23	<0.0001	3.25	1.85-5.72	<0.0001

RR, relative incidence ratio; CI, confidence interval.

[a] Relative incidence ratios could not be calculated for the period 1991-2000 because of the low number of events in this time period.

PART II

Prediction



CHAPTER 6

Isolated ileal blind loop inflammation after intestinal resection with ileocolonic anastomosis in Crohn's disease: an often neglected endoscopic finding with an unfavorable outcome

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Abstract

Objective

Postoperative endoscopic recurrence in patients with Crohn's disease (CD) is commonly classified using the Rutgeerts score. Ulcerations in the ileal blind loop are not taken into account in the Rutgeerts score, and the clinical relevance of these lesions is unknown. This study aimed to assess the outcome of isolated ileal blind loop inflammation (IBLI) in postoperative CD patients.

Methods

Adult CD patients who underwent intestinal surgery with ileocolonic anastomosis between 1997 and 2017 were included and postoperative endoscopy reports were retrospectively reviewed. IBLI was defined as isolated inflammation of the ileal blind loop with or without ulcera confined to the anastomosis. Outcome was assessed using endoscopic recurrence (Rutgeerts >i2) and surgical recurrence (re-resection).

Results

A total of 341 CD patients were included. In 125 out of 341 (37%) patients, the ileal blind loop was described in the endoscopy reports. IBLI was reported in 43 of 341 (13%) patients. Start or step-up drug therapy was initiated in 10 of 32 (31%) IBLI patients with abdominal symptoms within a median of 0.9 months [interquartile range (IQR) 0.7–1.4] after ileocolonoscopy. Endoscopic recurrence occurred in 4 out of 38 (11%) IBLI patients without re-resection, within a median of 12.4 months (IQR 6.8–13.3). Intestinal re-resection was performed in 5 out of 43 (16%) IBLI patients within a median of 3.7 months (IQR 3.5–10.8).

Conclusion

IBLI is associated with symptoms and an unfavorable outcome, with a high risk of endoscopic recurrence in the neoterminal ileum and intestinal re-resection during short-term follow-up. Therefore, the blind ileal loop needs to be assessed during endoscopy in postoperative CD patients.

Introduction

Intestinal surgery is a valuable treatment option in patients with Crohn's disease (CD). Intestinal resection rates in CD patients are estimated at 50–70% within 10 years after diagnosis.[1,2] Patients with ileal or ileocolonic CD localization have a higher likelihood of undergoing intestinal resection, with hazard ratios (HRs) of 3.4 and 3.3 respectively, when compared with isolated colonic disease localization.[2,3] Consequently, most frequently performed surgeries in CD patients are ileocecal resections or right hemicolectomies with ileocolonic anastomosis.[2,4]

The benefits of surgery are substantial, and a recent randomized controlled trial demonstrated ileocolonic resection to be an alternative to step-up therapy with TNFα-blockers with regard to patient reported quality of life.[5] However, postoperative recurrence is highly prevalent, with endoscopic lesions recurring in up to 80% of patients within 1 year.[6,7] Current postoperative treatment strategies aim at prevention, early detection and early medical treatment of endoscopic lesions.[8,9] In particular, publication of the Rutgeerts score as a tool to classify endoscopic lesions has influenced postoperative treatment and follow-up strategies. In the landmark study from Rutgeerts *et al.*, the clinical recurrence rates 5 years after endoscopy were assessed in 89 postoperative CD patients, and estimated at 10% for Rutgeerts score of i0 or i1, 25% for Rutgeerts score i2, 60% for Rutgeerts score i3 and 100% for Rutgeerts i4.[6]

Following the observation of mucosal lesions preceding clinical symptoms, the Rutgeerts score at ileocolonoscopy has gained a central role in guiding decisions on drug therapy in postoperative CD patients. Pre-emptive ileocolonoscopy early after intestinal resection is recommended in international guidelines.[9,10] A randomised trial confirmed the importance of early ileocolonoscopy after 6 months and subsequent step-up drug therapy for endoscopic recurrence, as endoscopic recurrence rates after 18 months were significantly lower compared to patients with conventional drug therapy without colonoscopy.[8]

Although the Rutgeerts score is a convenient tool during postoperative endoscopy and widely used to estimate the risk of recurrence, it has some limitations. Currently, a side-to-side ileocolonic anastomosis is most often used during CD surgery. As end-to-end anastomosis was common at the time of publication of the original Rutgeerts score, assessment of the Rutgeerts score is limited to the anastomosis and neoterminal ileum, while the blind ileal loop is not taken into account. The prevalence and outcome of isolated inflammation of the ileal blind loop are unknown. In this study, we aimed to assess the occurrence of isolated ileal blind loop inflammation, associated risk factors and outcomes in postoperative CD patients.

Materials and methods

Study population

This multicenter, retrospective study was performed in the Erasmus MC, Rotterdam (academic center) and in the Amphia hospital, Breda (large teaching hospital). All adult CD patients (aged ≥18 years) who underwent an intestinal resection with ileocolonic anastomosis between January 1997 and June 2017 were included. The study population was identified using Endobase (Olympus corp. Tokyo, Japan), a hospital endoscopy registry system in which the type of endoscopy, the indication and the endoscopy report are stored.[11] In this endoscopy registry, a search was performed using the terms ('Crohn' and 'resection') or 'anastomosis' or 'Rutgeerts' or 'ileocecal'. Subsequently, all hospital records of the obtained patient population were hand searched for the date of surgery.

Data collection

Endoscopy reports of the selected patients were reviewed and endoscopic findings at the ileocolonic anastomosis were registered. Ileal blind loop inflammation (IBLI) was defined as isolated inflammation (erosions and/or ulcerations) of the ileal blind loop with or without aphtous ulcers confined to the anastomosis. CD patients after ileocolonic resection without IBLI were selected as background population. Patient and disease characteristics including demographics, disease phenotype and duration, smoking status and surgical history were collected from hospital records. Clinical charts were reviewed for the indication of colonoscopy and the presence of symptoms (increased stool frequency and/or abdominal pain) at the time of IBLI diagnosis. The start or step-up of CD medication within 3 months after IBLI diagnosis was recorded. Follow-up data including performed endoscopies and subsequent surgeries were collected up to June 2017.

Outcome measures

Endoscopic recurrence was defined as extension of IBLI to the neoterminal ileum with Rutgeerts score i3 or i4, and surgical recurrence was defined as an intestinal re-resection.

Data analysis

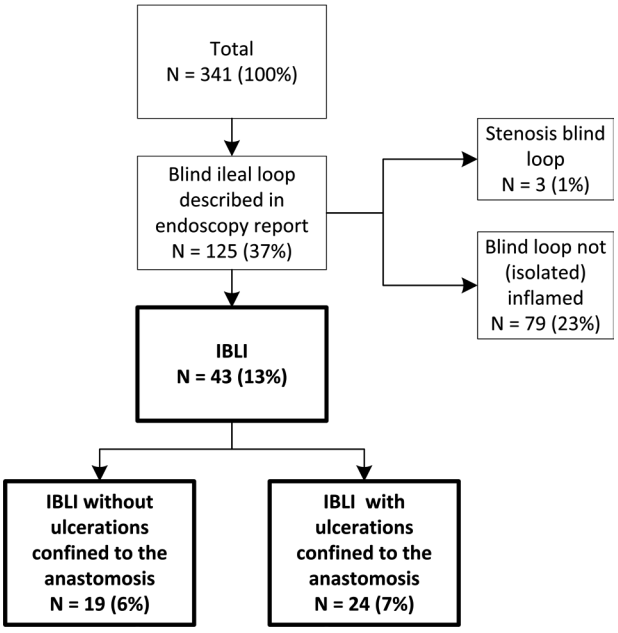
IBM SPS Statistics version 24.0 (IBM Corp. Released 2013, IBM Corp, Armon, New York) was used for statistical analysis. Continuous variables were described as medians and compared using Mann–Whitney U test. Categorical variables were described using proportions and percentages and compared using χ^2 test. Survival statistics using Kaplan–Meier analysis was used to describe occurrence and time to IBLI diagnosis. The index date for survival analysis for the IBLI population was the date of the last surgery after which IBLI was observed. For the background population, the most recent surgery was selected as index date. Associated factors for IBLI were identified using Cox proportional hazard analysis. A *P*-value of <0.05 was accepted as statistically significant.

This study was conducted in accordance with the protocol and the principles of the Declaration of Helsinki. The study protocol was approved by the Medical Ethical Review Committee of the Erasmus University Medical Center on the 16th of August 2017.

Results

In total, 341 [132 male (39%)] postoperative CD patients were included. The ileal blind loop was described in the endoscopy report in 125 (37%) patients. IBLI was reported in 43 of 341 (13%) patients, of whom 19 (6%) patients had ulcerations limited to the blind loop, and 24 (7%) patients had IBLI combined with aphthous ulcers confined to the anastomosis. **Figure 1.** The main indication for the endoscopy revealing IBLI was symptoms in 26 (60%) IBLI patients, followed by standard work-up after intestinal resection in 9 (21%) IBLI patients and effect monitoring of medical therapy in eight (19%) IBLI patients.

Figure 1. Flow chart of IBLI occurrence.



IBLI, ileal blind loop inflammation.

The baseline characteristics in the IBLI population (n = 43) showed no significant differences to the background population (n = 298), with regard to sex, Montreal classification and smoking status. Family history of IBD was positive in 15 out of 43 (35%) IBLI patients, which was significantly more frequent compared to 57 of 298 (19%) patients in the background cohort (P = 0.002). Furthermore, a significantly higher proportion of IBLI patients, 16/43

(37%) vs. 67/298 (23%) in the background population, had undergone multiple previous ileocolonic resections, *P* = 0.035. **Table 1.**

Table 1. Baseline characteristics

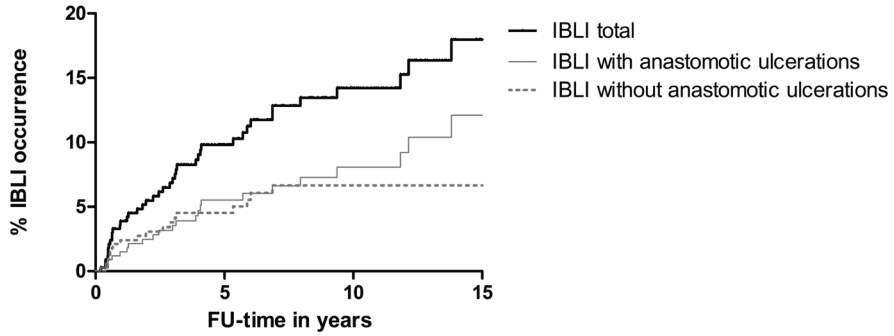
		IBLI (n=43)	Background (n=298)	P-value
Male sex n(%)		19(44)	113(38)	0.430
Family history of IBD n(%)		15(35)	57(19)	0.002
Montreal A n(%)	<17 yr	4(10)	43(14)	0.618
	17-40 yr	32(74)	203(68)	
	>40 yr	7(16)	52(18)	
Montreal L n(%)	Ileum	20(47)	131(44)	0.889
	Colon	0(0)	11(4)	
	Ileocolonic	23(53)	156(52)	
Montreal B n(%)	Luminal	15(35)	135(45)	0.294
	Stricturing	23(53)	122(41)	
	Penetrating	5(12)	41(14)	
Peri-anal disease n(%)		6(14)	67(22.5)	0.196
Smoking n(%)		23(54)	138(46)	0.270
Ileocolonic resections n(%)	1	27(63)	231(77)	0.035
	>1	16(37)	67(23)	
Time from resection to endoscopic evaluation in years, median(IQR)		2.9 (0.7-5.9)	1.5 (0.6 – 4.8)	0.092

IBLI, ileal blind loop inflammation

Risk of ileal blind loop inflammation

The median time between the last resection and description of IBLI in the endoscopy report was 2.9 years [interquartile range (IQR) 0.7–5.9] and the majority of IBLI cases (69.8%) occurred in the first 5 years after resection. Kaplan–Meier survival analysis showed that 5 years after the most recent intestinal resection, IBLI was described in the endoscopy report of 5.8% of the population. After 10 years, IBLI was described in 14.2% of the patients at risk. IBLI without anastomotic ulcers was described in 4.5% and 6.7% of patients, after 5 and 10 years, respectively. **Figure 2**

Figure 2. Kaplan–Meier survival curve representing the percentage of IBLI occurrence during follow-up time after the most recent intestinal resection.



	0 years	5 years	10 years	15 years
Patients at risk	341	208	104	43

IBLI, ileal blind loop inflammation; FU-time, follow-up time

Consistent with the observed baseline characteristics, in univariable analysis, a positive family history of IBD [HR 3.7, 95% confidence interval (CI) 1.8–7.8] and multiple previous ileocolonic resections (HR 2.3, 95% CI 1.2–4.3) were identified as factors associated with the occurrence of IBLI. In multivariable analysis, a positive family history of IBD remained a significant risk factor, HR 3.5, 95% CI 1.5–7.4 (P < 0.001). **Table 2.**

Clinical manifestation

A total of 32 out of 43 (74%) IBLI patients [14/19 (74%) IBLI without anastomotic ulcers and 18/24 (75%) IBLI with anastomotic ulcers] complained of abdominal pain and/or increased bowel movements at the time of endoscopy revealing IBLI. Subsequent start or step-up drug therapy was initiated in 10 out of 32 (31%) symptomatic patients [5/14 (36%) true IBLI and 5/18 (27%) IBLI with anastomotic ulcers], within a median of 0.9 months (IQR 0.7–1.4) after colonoscopy. The following therapies were initiated: mesalazine (one patient), budesonide (five patients), azathioprine (one patient) and anti-TNFα therapy (three patients). In one patient who underwent standard colonoscopy for recurrent inflammation, without clinical symptoms, budesonide was initiated after the diagnosis of IBLI.

Outcome

Extension of inflammation to the neoterminal ileum (Rutgeerts score i3 or i4) occurred in 4 out of 38 (11%) patients without a subsequent resection during follow-up, within a median of 12.4 months (IQR 6.8–13.3) after IBLI diagnosis. Endoscopic recurrence in the background population was comparable, 45 out of 298 (15%) (P = 0.452), although the time to recurrence, within a median of 42.8 months (IQR 16.7–90.2), was significantly longer compared to IBLI patients (P = 0.013). Median total follow-up time was also significantly

shorter in the IBLI cohort, median 1.9 years (IQR 0.9–4.4), compared to 7.0 years (IQR 3.9–12.1) in the background cohort ($P < 0.001$).

Table 2. Hazard ratios of factors possibly associated with IBLI in univariable and multivariable regression analysis

		Univariable analysis			Multivariable analysis		
		HR	95% CI	P	HR	95% CI	P
Male sex		1.2	0.7-2.4	0.408			
Montreal A	**< 17 yr**	1	Ref	Ref			
	17-40 yr	1.9	0.7-5.3	0.232			
	> 40 yr	1.6	0.5-5.4	0.463			
Montreal L	**Ileum**	1	Ref	Ref			
	Ileocolonic	0.8	0.5-1.6	0.666			
Montreal B	**Luminal**	1	Ref	Ref			
	Stricturing	1.6	0.8-3.0	0.168			
	Penetrating	1.2	0.4-3.3	0.741			
Peri-anal disease		0.5	0.2-1.3	0.164			
Active or previous smoking		1.4	0.7-2.8	0.312			
IBD family history		3.7	1.8-7.8	**<0.001**	3.5	1.6-7.4	**<0.001**
Time from diagnosis to first resection		1.0	0.9-1.1	0.256			
Age at first resection		1.0	0.9-1.0	0.676			
Multiple ileocolonic resections		2.3	1.2-4.3	**0.009**	1.4	0.6-3.2	0.376

IBLI, ileal blind loop inflammation. HR, Hazard Ratio. CI, Confidence Interval.

In five patients (16%), clinical symptoms led to a subsequent resection during follow-up after IBLI diagnosis, within a median of 3.7 months (IQR 3.5–10.8). Three of these re-resections were revisions of the ileocolonic anastomosis, after which all three patients experienced an immediate relieve of symptoms.

Discussion

The blind ileal loop at the ileocolonic anastomosis after intestinal resection in CD is erroneously disregarded. In this study, we have shown that a description of the ileal blind loop is lacking in nearly two-thirds of endoscopy reports in postoperative CD patients with a side-to-side ileocolonic anastomosis. This finding is in sharp contrast to our results that demonstrate an unfavorable disease course after IBLI diagnosis, with regard to a considerable risk of endoscopic recurrence and surgical re-resection, both at short-term follow-up. Furthermore, despite its association with symptoms, drug therapy is infrequently initiated or changed after IBLI diagnosis.

To the best of our knowledge, this study is the first to assess the occurrence rate and prognosis of IBLI. The side-to-side anastomosis is the preferred technique in ileocolonic CD surgery after evidence of an advantage for the wider side-to-side when compared to end-to-end or end-to-side anastomosis in terms of anastomotic leakage, CD recurrence and re-resection risk.[12–15] Therefore, endoscopists are familiar with the anatomy of the side-to-side ileocolonic anastomosis. Nevertheless, we observed that a description of the ileal blind loop is missing in the majority of endoscopy reports. As a consequence, this retrospective cohort provides insufficient data to give an accurate estimation of IBLI prevalence. Considering that a description of the blind loop is often lacking in endoscopy reports, IBLI occurrence might yet be underestimated. Hence, the detection rate of IBLI needs to be confirmed in a larger prospective study.

The etiology of IBLI is unknown, and may be different from the etiology of recurrent CD lesions in the neoterminal (afferent) ileum. Hypotheses that warrant consideration include ischemia, disturbance of the microbiome by fecal stasis and diversion ileitis. The first potential mechanism underlying IBLI might be ischemia in the top of the blind loop, similar to the suggested pathophysiology of recurring ulcers confined to the anastomosis (Rutgeerts score i2a) [16]. Second, stasis of bowel content may cause bacterial overgrowth, similar to diarrhea caused by blind loop syndrome after bariatric surgery.[17,18] Although small intestinal bacterial overgrowth has previously been observed in CD patients,[19] it has never been linked to the development of endoscopic ulcers. Third, diversion ileitis may be the most plausible etiology of IBLI. Diversion of the fecal stream could induce inflammation, similar to diversion colitis. The pathophysiology of diversion colitis is not fully elucidated, and may be a combination of ischemia caused by a shortage of short chain fatty acids causing increased arteriolar resistance and dysbiosis.[20] Current insights in the pathogenesis of CD advocate an important role for the decreased diversity of the gut flora in the perpetuating activation of inflammation.[21] Also in the setting of postoperative CD, early studies have suggested an important influence of the microbiota by demonstrating a benefit of metronidazole in the prevention of postoperative CD recurrence.[22] More recent studies showed microbiome diversity was decreased after CD surgery,[23] and alterations in gut microbiota distribution around the anastomosis were associated with postoperative endoscopic recurrence.[24] The microbiome in the blind ileal loop needs to be further studied. In this respect, the length of the created ileal blind loop could be of interest, as a long segment may be associated with dysbiosis. Unfortunately, details on the length of the ileal blind loop in our series are lacking. Our results showed that three patients became asymptomatic after surgical revision of the side-to-side anastomosis, which supports that the anatomical composition of the side-to-side anastomosis could be relevant in the development of IBLI.

Known risk factors associated with postoperative endoscopic recurrence in the neoterminal ileum, for example, smoking and penetrating disease[9,25] were not associated with IBLI in our

study. Significantly more IBLI patients had undergone multiple resections before baseline. Although this factor was not significantly associated with IBLI in multivariable analysis, it might suggest a more aggressive disease course and could have contributed to a higher postoperative recurrence rate in IBLI patients. Further assessment in a larger cohort is necessary to provide a balanced analysis of this potential confounding factor. In our study, a positive family history for IBD was the only factor significantly associated with IBLI in multivariable analysis. Hypothetically, the association between a positive IBD family history and IBLI in postoperative CD patients might be explained by gene variations that play a role in microbiome dysbiosis. For instance, *NOD2* gene mutations are common in CD familial heredity and are associated with a deficient antimicrobial response and immune regulatory dysfunction.[26–28]

IBLI patients seem to have an unfavorable prognosis considering high re-resection rates within a short time period after IBLI diagnosis. Endoscopic progression of the inflammation to the neoterminal ileum (i.e. Rutgeerts score i3/i4) was observed in 11% within 5 years. In the background population, we observed progression to Rutgeerts score i3/i4 within 5 years in 5% for Rutgeerts score i2a at first postoperative endoscopy, and 60% for Rutgeerts score i2b. It could be speculated that IBLI should be placed between i2a and i2b in a revised Rutgeerts score. However, the timing of the endoscopies in both groups in this study differs considerably and a firm conclusion cannot be drawn. Future prospective research with standardized timing of colonoscopies is needed before adding IBLI to a revised Rutgeerts score.

This retrospective study, assessing detailed information collected from endoscopy reports and hospital charts of an academic center and a large teaching hospital, serves as a plea for further prospective evaluation of IBLI, with regard to pathophysiology, prevalence and prognosis. Evidently, a few limitations of this study, inherent to its retrospective design, need to be considered. First, patients were not followed or treated according to a standardized follow-up protocol. This might have led to an underestimation of IBLI occurrence, since the majority of endoscopies were performed on indication of symptoms. Furthermore, the index date differed between both cohorts. For IBLI patients, the index date was the last surgery before the endoscopy revealing IBLI, while in the background population the last surgery overall was chosen. Although the index dates were deliberately determined to allow for the most reliable and accurate comparison between both cohorts, follow-up and outcome results need to be interpreted with care. Nonetheless, our retrospective data enable interpretation of the results in a real-world setting, which provides insight in the occurrence and consequences of IBLI in everyday clinical practice. Second, endoscopy reports were not uniform and endoscopists might have assessed the ileal blind loop during postoperative endoscopy, but might not have included a description in the endoscopy report. Especially during earlier follow-up years, when endoscopy reports were less

standardized and guidelines on postoperative endoscopies were not yet published, blind loop assessments might have been underreported in our study. A sensitivity analysis regarding the outcome endoscopic recurrence was performed in a selection of patients with a description of the blind loop in the endoscopy report (n = 125), which showed an overall increase from 15 to 19% endoscopic recurrence in the background population compared to 11% in IBLI patients, P = 0.181. Third, because IBLI was described more often in endoscopy reports from more recent calendar years, total follow-up time was shorter in the IBLI cohort as compared to the background cohort, hampering interpretation of the comparison of endoscopic recurrence between both cohorts. Shorter follow-up might have led to lower endoscopic recurrence rates. Finally, the study population was too small to allow for in-depth analysis of risk factors for IBLI.

In conclusion, the blind ileal loop is often disregarded during postoperative ileocolonoscopy. Nevertheless, it is associated with symptoms and this study suggests an unfavorable prognosis of IBLI, as a high risk of surgical recurrence during follow-up was observed. Therefore, the blind ileal loop needs to be assessed during endoscopy in postoperative CD patients with ileocolonic anastomosis, both in clinical practice and in prospective research.

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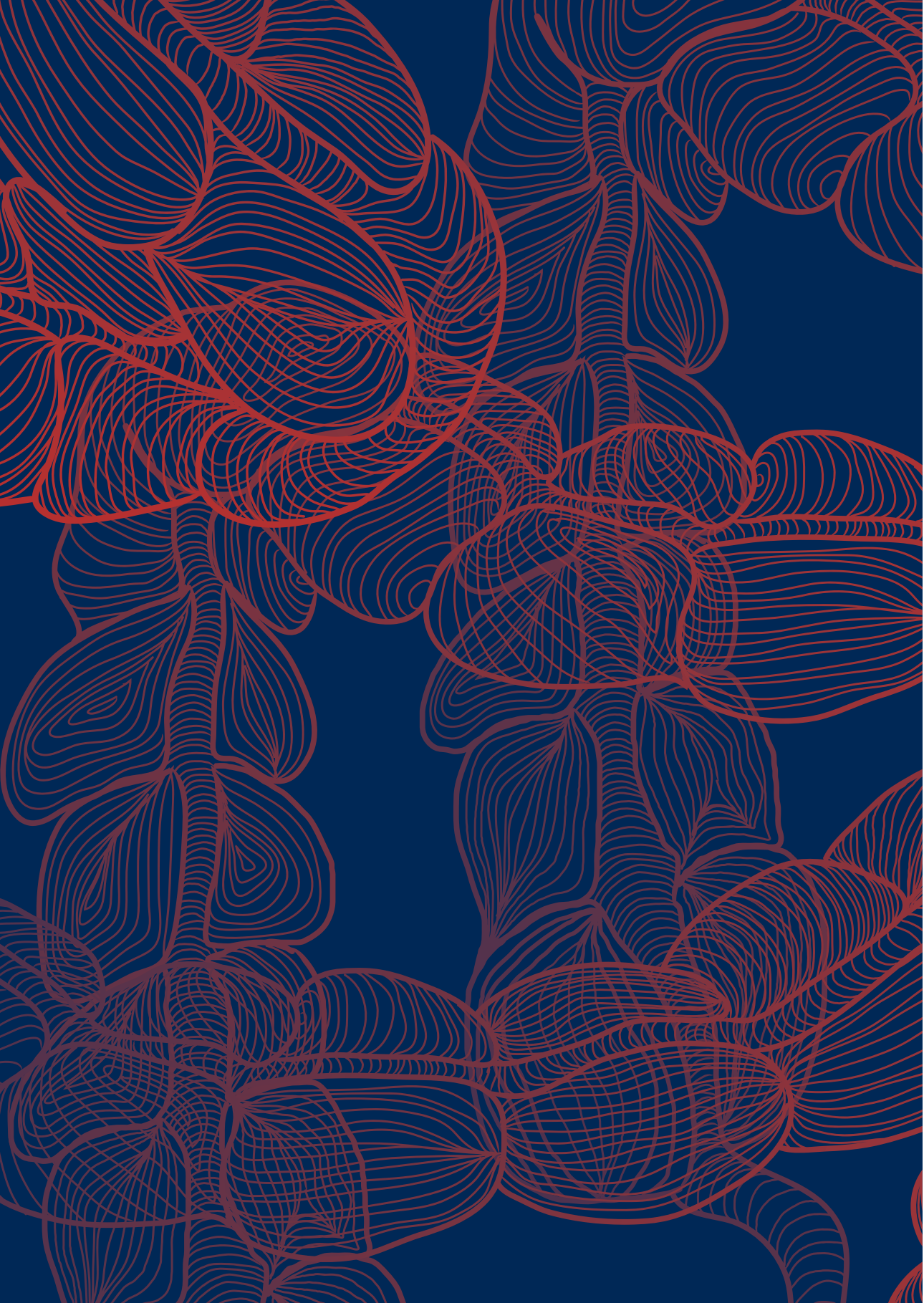

CHAPTER 9

Risk prediction and comparative efficacy of anti-TNF vs thiopurines, for preventing postoperative recurrence in Crohn's Disease: a pooled analysis of 6 trials

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Abstract

Background & Aims

The superiority of anti-TNF-α agents to thiopurines for the prevention of postoperative recurrence of Crohn's disease (CD) after ileocolonic resection remains controversial. In this meta-analysis of individual participant data (IPD), the effect of both strategies was compared and assessed after risk stratification.

Methods

After a systematic literature search, IPD were requested from randomized controlled trials investigating thiopurines and/or anti-TNF-α agents after ileocolonic resection. Primary outcome was endoscopic recurrence (ER) (Rutgeerts score ≥i2) and secondary outcomes were clinical recurrence (Harvey-Bradshaw Index/Crohn's Disease Activity Index score) and severe ER (Rutgeerts score ≥i3). A fixed effect network meta-analysis was performed. Subgroup effects were assessed and a prediction model was established using Poisson regression models, including sex, smoking, Montreal classification, CD duration, history of prior resection and previous exposure to anti-TNF-α or thiopurines.

Results

In the meta-analysis of IPD, 645 participants from 6 studies were included. In the total population, a superior effect was demonstrated for anti-TNF-α compared with thiopurine prophylaxis for ER (relative risk [RR], 0.52; 95% confidence interval [CI], 0.33–0.80), clinical recurrence (RR, 0.50; 95% CI, 0.26–0.96), and severe ER (RR, 0.41; 95% CI, 0.21–0.79). No differential subgroup effects were found for ER. In Poisson regression analysis, previous exposure to anti-TNF-α and penetrating disease behavior were associated with ER risk. The advantage of anti-TNF-α agents as compared with thiopurines was observed in low- and high-risk groups.

Conclusions

Anti-TNF-α is superior to thiopurine prophylaxis for the prevention of endoscopic and clinical postoperative CD recurrence after ileocolonic resection. The advantage of anti-TNF-α agents was confirmed in subgroup analysis and after risk stratification.

Introduction

Intestinal resection is an important treatment modality in Crohn's disease (CD) and is performed in up to 70% of patients during the disease course.[1-3] Ileocecal resection is a valuable option when CD is limited to the terminal ileum or ileocecal region, associated with comparable quality of life and cost-effectiveness as compared with step-up to anti-tumor necrosis factor (TNF) therapy at 12-month follow-up.[4,5] In addition, intestinal resection may induce long-term remission and provides immediate relief of symptoms. Nevertheless, intestinal resection in CD is not curative, and postoperative CD recurrence after ileocolonic resection is common.[6,7] Despite prophylactic medication and standardized postoperative endoscopic evaluation after ileocolonic resection, endoscopic recurrence at or proximal to the ileocolonic anastomosis (Rutgeerts score ≥i2) occurs in up to 50% of patients at 18 months.[8,9]

Several studies have investigated the efficacy of CD medication for the prevention of postoperative recurrence. Prophylactic mesalamine was not proven to be more effective than placebo.[10,11] In addition, antibiotics, such as metronidazole, were associated with lower short-term recurrence rates, although the effect was not sustained long-term and considerable rates of intolerance were reported.[12,13]

Current European and American guidelines recommend starting prophylactic postoperative medication with thiopurines or anti-TNF-α agents in CD patients at high risk of postoperative recurrence. Although both guidelines propose a slightly different definition of high risk, they are consistent on the risk factors of smoking, prior intestinal resection, and penetrating disease behavior.[1,14,15] Available guidelines do not express a preference for either anti-TNF-α or thiopurines in postoperative CD patients.

Studies directly comparing the efficacy of thiopurines and anti-TNF-α agents in postoperative setting are scarce and show conflicting results.[16-18] Recent network meta-analyses have reported anti-TNF-α therapy to be superior to thiopurines in the prevention of postoperative recurrence.[19,20] However, interpretation of these results is hindered by variation in included studies, with differences in concomitant medication use, outcome definitions, and length of follow-up.

To overcome the disadvantages of network analyses of published data, we aimed to perform a meta-analysis of individual participant data (IPD) in the original study databases of the trials to compare the effect of thiopurines and anti-TNF-α agents for prevention of postoperative CD recurrence in different subpopulations.

Materials and methods

The study protocol was approved by the Medical Ethical Review Committee of the Erasmus University Medical Center and is registered in the PROSPERO register, number CRD42019131606. This meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21,22]

Selection criteria

Eligible studies were randomized controlled trials including adult (≥18 years of age) CD patients who underwent ileocolonic resection and assessed the effect of anti-TNF-α vs thiopurine therapy, or assessed the effect of 1 of both therapies vs placebo or mesalamine. Study medication had to be started within 3 months after ileocolonic resection for the prevention of postoperative CD recurrence. Concomitant medication use was only allowed when prescribed (standardized) to patients in both the anti-TNF-α and thiopurine treatment arms. Excluded were studies in which CD therapy was started after postoperative recurrence was diagnosed, studies testing the optimal dosing of the same medication without control arm, studies investigating the effect of antibiotics as monotherapy, and studies comparing agents of the same drug class (eg, adalimumab vs infliximab).

Search strategy

A comprehensive systematic search was designed in collaboration with the Medical School Library of the Erasmus University Rotterdam and was conducted in Embase, Medline, Web of Science, the Cochrane database, and Google Scholar. The search was conducted using controlled vocabulary supplemented with key words. **Supplementary data**. The retrieved studies were screened and selected based on previously mentioned inclusion and exclusion criteria by 2 independent reviewers (E.M.J.B. and J.H.C.A.).

Risk-of-bias and quality-of-evidence assessment

Risk of bias was assessed by 2 investigators (E.M.J.B. and J.H.C.A.) using the Cochrane Collaboration risk-of-bias tool for randomized clinical trials.[23] The GRADE considerations were used to assess quality of evidence.[24] Any discrepancies were resolved by consensus within the research team.

IPD database

For each selected trial, corresponding authors were contacted to request IPD. Data were de-identified before sharing. Participants who received concomitant therapy of thiopurine and anti-TNF-α at baseline, participants with isolated colonic disease location (prior to ileocolonic resection), and participants who had undergone other types of intestinal resection than ileocolonic resection were excluded from the IPD database.

Data collection

Medication regimen, population size, study duration, and outcome definitions were described for each trial. IPD for the following variables were extracted: age, gender, CD disease duration, Montreal classification for CD, smoking status, prior surgeries, previous CD medication exposure, concomitant medication, endoscopic recurrence and Rutgeerts score, clinical recurrence, and re-resection.

Outcome parameters

The primary outcome was endoscopic recurrence, defined by a Rutgeerts score of i2 or higher at postoperative endoscopy. Secondary outcomes were clinical recurrence, defined by Crohn's Disease Activity Index >200 (CDAI) or Harvey-Bradshaw Index ≥8, and severe endoscopic recurrence, defined by a Rutgeerts score of i3 or higher at postoperative endoscopy.

Statistical analysis

Network Meta-Analysis

A fixed-effects network meta-analysis was established using a Poisson regression model to adjust for differences in length of study by including the natural logarithm of follow-up time of a patient as an offset term in the model. The network meta-analysis combined studies directly comparing anti-TNF-α and thiopurines as well as studies comparing anti-TNF or thiopurines with a different treatment (placebo or mesalamine).

Subgroup analysis

Potential differential subgroup effects were investigated by fitting Poisson regression models in all participating studies, including a stratified intercept for the original randomized controlled trial, treatment variable, subgroup, interaction between subgroup and treatment, and the logarithm of time of follow-up as an offset variable.

Prediction model and treatment effect across risk groups

To assess whether the treatment effect of anti-TNF-α vs thiopurine differed across patients, we additionally followed an effect modeling approach[25] in all participating studies. First, a prediction model estimating the risk of recurrence was developed using a Poisson regression model. Variables included in Poisson regression analysis were smoking, disease behavior according to Montreal classification, disease localization according to Montreal classification, CD duration, previous anti-TNF-α exposure, previous thiopurine exposure, and prior surgery in medical history. Backward selection with a liberal $P > .20$ was used to reduce the number of variables in the model. We defined low- and high-risk groups of recurrence and assessed whether differential relative or absolute treatment effect across different risk strata were present. Data were analyzed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), and the network meta-analysis models were fitted using a Bayesian model via JAGS.

Results

The systematic search retrieved 2294 unique studies, of which 9 studies fulfilled eligibility criteria. IPD were obtained from 6 studies, including a total of 837 participants. Postoperative endoscopy data were available in 5 of 6 randomized controlled trials. Figure 1. Studies of which no IPD were received are displayed in Supplementary table 1, Supplementary data. Three of the included studies directly compared thiopurines and anti-TNF-α therapy,[16,17,26] and 3 studies compared 1 of both therapies with placebo or mesalamine. Table 1.[27, 28, 29]

Figure 1. Flow chart of study selection

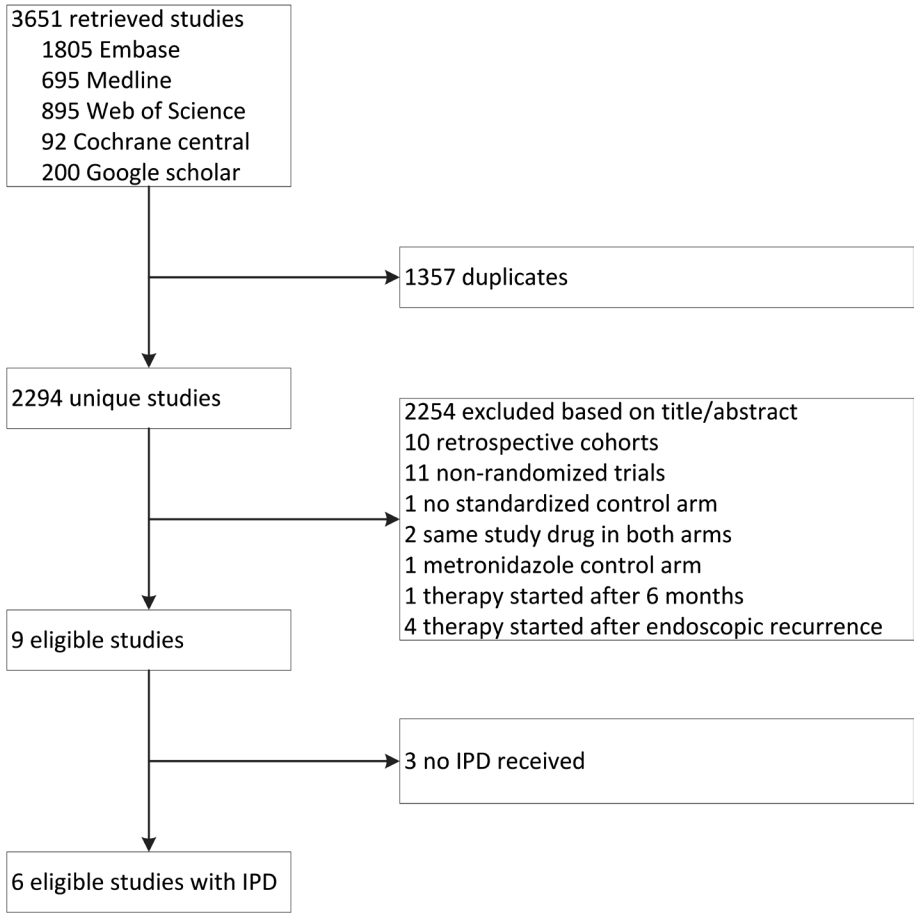


Table 1. Characteristics of included studies

Study	Country	Medication type and dose		Eligible patients (N)	Study period	Clinical recurrence	Endoscopic recurrence	Total FU
Ardizzone. Gastroenterology, 2004[29]	Italy	AZA	2 mg/kg/d	30	1994 – 2001	CDAI > 200	-	104 w
		5ASA	3 g/d	40				
Armuzzi. JCC, 2013[16]	Italy	IFX	5 mg/kg/8w	11	2007 – 2011	HBI ≥8	≥i2 at 52 w	52 w
		AZA	2.5 mg/kg/d	10				
Lopéz-SanRoman. JCC 2017[17]	Spain	ADA	40 mg/2w	38	2012 – 2015	CDAI > 200	≥i2 at 52 w	52 w
		AZA	2.5 mg/kg/d	27				
Mowat. Lancet Gastro Hep, 2016[27]	UK	MP	1 mg/kg/d	124	2008 – 2012	CDAI > 200*	≥i2 at 49 w and 176 w	176 w
		Plac	-	109				
Regueiro. Gastroenterology, 2013[28]	USA, UK, Australia, Belgium, Czech Republic, France, Germany, Hungary, Israel, the Netherlands, Poland, Austria, Italy, Canada	IFX	5 mg/kg/8w	101	2010 – 2012	CDAI > 200*	≥i2 at 76 w	104 w
		Plac	-	104				
Savarino. Am J Gastroenterology, 2013[26]	Italy	ADA	40mg/2w	16	2008 - 2010	CDAI > 200	≥i2 at 52 and 104 w	104 w
		AZA	2 mg/kg/d	17				
		5ASA	3 g/d	18				

*and 100 points increase from baseline. AZA = azathioprine, 5ASA = 5-aminosalicylates, IFX = infliximab, ADA = adalimumab, MP = mercaptopurine, Plac = placebo, mg = milligram, kg = kilogram, g = gram, d = day, w = week, FU = follow-up

After assessment of IPD of the 6 included studies, a total of 151 patients were excluded: 48 patients because of the use of concomitant thiopurine, 41 patients who received concomitant mesalamine, 66 patients who did not undergo an ileocolonic resection, 9 patients who had isolated colonic disease prior to resection, and in 28 patients insufficient information was available (eg, owing to loss to follow-up) to establish an analysis of the outcome measures.

Characteristics of the study population

The final study population comprised 645 patients (316 [49.0%] male; median age at baseline 37.0 [interquartile range (IQR), 28.0–47.0] years). At baseline, 316 (49.9%) patients had isolated ileal disease and 317 (50.1%) had ileocolonic disease. The ileocolonic resection concerned a primary ileocecal resection in 401 (62.3%) patients and an ileocolonic re-resection in 242 (37.7%) patients. Behavior of disease, according to Montreal classification, was luminal or inflammatory in 111 (18.4%) patients, stricturing in 199 (33.0%) patients, and penetrating in 293 (48.6%) patients. Prior to surgery, 318 (49.3%) patients had been exposed to thiopurines and 140 (21.7%) patients to anti-TNF-α therapy. **Table 2**.

Postoperatively, 213 (33.0%) patients received placebo, 58 (9.0%) received mesalamine, 208 (32.3%) received thiopurine (84 [13.0%] azathioprine, 124 [19.2%] mercaptopurine), and 166 (25.7%) received anti-TNF-α therapy (54 [8.4%] adalimumab, 112 [17.4%] infliximab) Characteristics per study are displayed in **Supplementary table 2, Supplementary data**. Patient characteristics per type of study medication are displayed in **Supplementary table 3, Supplementary data.**

Risk-of-bias assessment

Two trials scored a high risk of bias because participants, caregivers, and outcome assessors were not blinded to treatment. These studies performed no analysis to investigate the effect of not blinding or deviating from the intended intervention. Two other trials raised some concerns with regard to bias, owing to not blinding the participants and caregivers. Additionally, 2 trials were assessed as low risk of bias. Details on the risk of bias assessment are provided in the Supplementary Material. **Supplementary figure 1, Supplementary data**.

Postoperative recurrence

A total of 132 (20.5%) of 645 patients developed clinical recurrence after a median of 53.1 (IQR, 33.7–85.4) weeks. Ileocolonoscopy was performed in 463 patients after a median of 76.4 (IQR, 50.4–104.0) weeks, during which endoscopic recurrence was diagnosed in 239 (51.6%) patients. During follow-up, 4 patients underwent intestinal re-resection.

Table 2. Patient characteristics

		N = 645
Male sex, N (%)		316 (49.0)
Age in years, median (IQR)		37 (28 – 47)
Active smoking, N(%)		173 (27.9)
	Missing	*25*
Disease duration in years, median (IQR)		2.8 (0.6 – 8.5)
	Missing, N	*215*
Montreal A, N (%)	< 17 years	21 (4.3)
	17-40 years	356 (73.4)
	> 40 years	108 (22.3)
	Missing, N	*160*
Montreal L, N (%)	Ileum	316 (49.9)
	Ileocolonic	317 (50.1)
	Missing, N	*12*
Montreal B, N (%)	Non-stricturing non-penetrating	111 (18.4)
	Stricturing	199 (33.0)
	Penetrating	293 (48.6)
	Missing, N	*42*
Prior intestinal resection in medical history, N (%)		243 (37.7)
	Missing, N	*1*
Previous thiopurine exposure, N(%)		318 (49.3)
Previous anti-TNFα exposure, N(%)		140 (21.7)
Study medication, N (%)	Placebo	213 (33.0)
	Mesalazine	58 (9.0)
	Thiopurine	208 (32.3)
	Anti-TNFα	166 (25.7)

Values are n (%), median (interquartile range), or n. TNF-α, tumor necrosis factor α.

Network meta-analysis

Network meta-analysis showed an advantage for anti-TNF-α prophylaxis as compared with thiopurine for endoscopic recurrence (relative risk [RR], 0.52; 95% confidence interval [CI], 0.33–0.80). For the secondary outcome measures of clinical recurrence and severe endoscopic recurrence, anti-TNF-α was also superior to thiopurine prophylaxis (RR, 0.50; 95% CI, 0.26–0.96; and RR, 0.41; 95% CI, 0.21–0.79, respectively).

Subgroup analysis

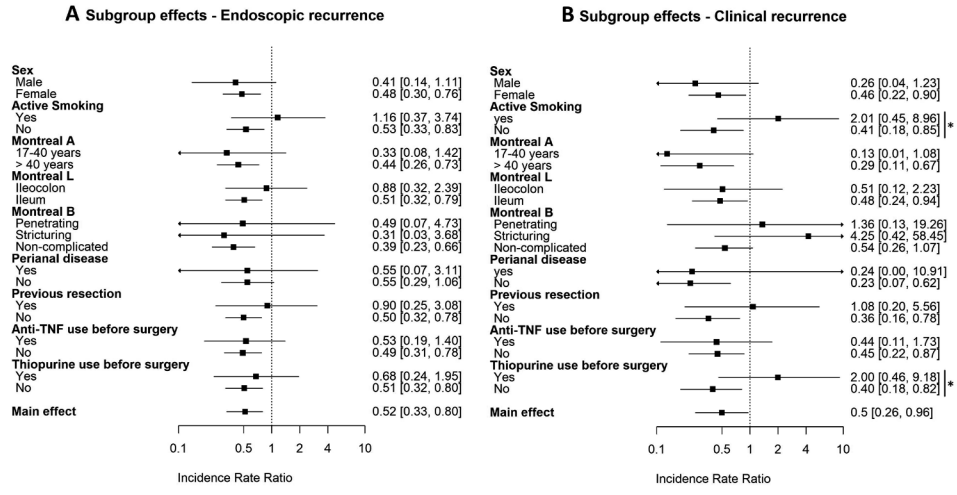
Effectiveness of anti-TNF-α and thiopurines was compared in different subgroups using network meta-analysis in all participating studies. For endoscopic recurrence, no significant differential subgroup effects could be demonstrated for gender, smoking, disease location according to Montreal classification, disease behavior according to Montreal classification,

perianal disease, history of prior intestinal resection, and previous exposure to anti-TNF-α or thiopurine. **Figure 2A**.

For clinical recurrence, a significant differential effect was found in smokers vs nonsmokers. In nonsmokers, patients on anti-TNF-α therapy were at significantly lower risk of postoperative clinical recurrence as compared with thiopurine users (RR, 0.41; 95% CI, 0.18–0.85), whereas in active smokers, the RR was 2.01 (95% CI, 0.45–8.96) for anti-TNF-α vs thiopurine. Corresponding 1-year absolute clinical recurrence rates were 0% for nonsmokers and 35% for smokers on anti-TNF-α vs 20% for nonsmokers and 40% for smokers on thiopurines. A differential subgroup effect was also found in patients with or without previous exposure to thiopurines (the RR was 0.40 [95% CI, 0.18–0.82] for thiopurine naïve vs 2.00 [95% CI, 0.46–9.18] for previous thiopurine exposure). Clinical recurrence rates at 1 year after ileocolonic resection were 6% for thiopurine-naïve patients and 6% for previous thiopurine-exposed patients on anti-TNF-α prophylaxis, as compared with 36% for thiopurine-naïve patients and 16% for previous thiopurine-exposed patients on thiopurine prophylaxis. **Figure 2B**.

For severe endoscopic recurrence, a differential subgroup effect was found in patients with ileocolonic (RR, 2.64; 95% CI, 0.56–13.0) vs ileal disease location (RR, 0.32; 95% CI, 0.14–0.69). Severe endoscopic recurrence rates at 1 year after ileocolonic resection were 9% for ileocolonic and 2% for ileal disease for anti-TNF prophylaxis, as compared with 16% for ileocolonic and 20% for ileal disease for thiopurine prophylaxis. **Supplementary figure 2, Supplementary data**.

Figure 2. Network meta-analysis of anti-TNF-α vs thiopurines in the prevention of postoperative recurrence in CD, in different subgroups. Presented are RRs and CIs for (A) endoscopic recurrence and (B) clinical recurrence.



∗Significant subgroup effect

Prediction model and treatment effect across risk groups

Endoscopic Recurrence

In Poisson regression analysis, previous exposure to anti-TNF-α (RR, 1.35; 95% CI, 1.01–1.81) and penetrating disease behavior (RR, 1.27; 95% CI, 0.90–1.78) were associated with endoscopic recurrence. In the risk model, patients who were exposed to anti-TNF-α prior to surgery or had penetrating disease behavior were considered at high risk, and all other patients were considered at low risk. In the low-risk group, the relative treatment effect of anti-TNF-α vs thiopurines was an RR of 0.38 (95% CI, 0.22–0.67) as compared with an RR of 0.76 (95% CI, 0.35–1.68) in the high-risk group. The difference in treatment effect was not statistically significant.

The probability of endoscopic recurrence at 1 year in the low-risk group was 9.9% for anti-TNF-α and 33.2% for thiopurines as compared with 19.8% and 59.7% in the high-risk group, respectively. **Figure 3A**. The corresponding absolute risk differences for endoscopic recurrence were 23.3% in low-risk patients and 39.9% in high-risk patients.

Clinical recurrence

Factors associated with an increased risk of clinical recurrence were prior intestinal resection in medical history (RR, 1.72; 95% CI, 1.23–2.41) and previous exposure to anti-TNF-α (RR, 1.64; 95% CI, 1.12–2.40). Factors protective of clinical recurrence were stricturing disease behavior (RR, 0.76; 95% CI, 0.48–1.18) and penetrating disease behavior (RR, 0.66; 95% CI, 0.43–1.01). In the risk model, patients were considered high risk if 2 or more of the risk factors noncomplicated disease, prior intestinal resection, and previous anti-TNF-α exposure were present. All other patients were considered low risk. In the low-risk group, the RR for clinical recurrence was 0.41 (95% CI, 0.08–1.53) for anti-TNF-α vs thiopurines, and in high-risk patients the RR was 0.47 (95% CI, 0.21–1.00). There was no significant difference in treatment effect between the low and high-risk group.

In the low-risk group, the absolute risk of clinical recurrence 1 year after ileocolonic resection was 3.7% for anti-TNF-α and 17.9% for thiopurines. In the high-risk group, clinical recurrence rates were 18.2% for anti-TNF-α and 27.3% for thiopurines. **Figure 3B**. The corresponding absolute risk difference for clinical postoperative recurrence between patients receiving prophylactic anti-TNF-α and prophylactic thiopurines was 14.2% in the low-risk group and 9.1% in the high-risk group.

Severe endoscopic recurrence

Previous exposure to anti-TNF-α (RR, 1.36; 95% CI, 0.91–2.02), prior intestinal resection (RR, 1.41; 95% CI, 0.99–2.01), and penetrating disease (RR, 1.41; 95% CI, 0.87–2.28) were associated with severe endoscopic recurrence. In the model, patients considered high risk if 2 or more factors were present. In the low-risk group, the relative treatment effect of anti-

TNF-α vs thiopurines was an RR of 0.31 (95% CI, 0.09–0.89) vs an RR of 0.35 (95% CI, 0.12–0.96) in the high-risk group. Absolute risk of severe endoscopic recurrence at 1 year in the low-risk group was 4.9% for anti-TNF-α vs 11.4% for thiopurines, and in the high-risk group it was 15.7% for anti-TNF-α vs 21.0% for thiopurines. **Figure 3C**. Corresponding absolute risk differences were 6.5% in low-risk patients and 5.3% in high-risk patients.

Summary of findings

Owing to risk of bias, the quality of evidence according to GRADE was scored as moderate for endoscopic recurrence. Owing to risk of bias and imprecision, the quality of evidence according to GRADE was scored as low for clinical recurrence. A grade summary of findings is provided in **Table 3**.

Figure 3. (A) The proportion of postoperative endoscopic recurrence 1 year after resection after prophylactic treatment with anti-TNF-α vs thiopurine, stratified in the low-risk group (no risk factor) and high-risk group (previous anti-TNF-α exposure and/or penetrating disease). (B) The proportion of postoperative clinical recurrence 1 year after resection after prophylactic treatment with anti-TNF-α vs thiopurine, stratified in the low-risk group and high-risk group (2 or more of the risk factors: prior intestinal resection, previous anti-TNF-α exposure, nonstricturing nonpenetrating disease). (C) The proportion of postoperative severe endoscopic recurrence 1 year after resection after prophylactic treatment with anti-TNF-α vs thiopurine, stratified in the low-risk group and high-risk group (2 or more of the risk factors: prior intestinal resection, previous anti-TNF-α exposure, and penetrating disease).

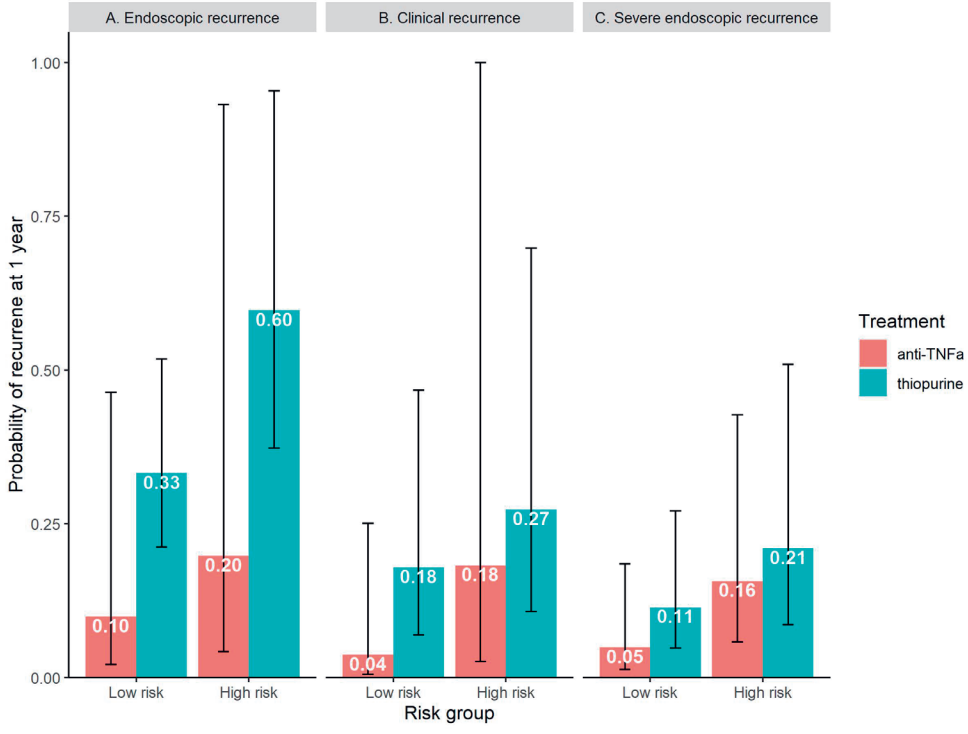


Table 3. GRADE summary of findings table

Outcome	Number of participants (studies)	Relative effect anti-TNFα vs thiopurine (95% CI)	Anticipated absolute effects in study population at 1 year (95% CI)				Quality (GRADE)	Comments
			Risk with anti-TNFα		Risk with thiopurine			
			Low risk	High risk*	Low risk	High risk*		
Endoscopic recurrence	463 (5 RCTs)	RR 0.52 (0.33 – 0.80)	99 per 1000 (21 - 464)	198 per 1000 (42 – 932)	332 per 1000 (212 - 518)	597 per 1000 (373 – 954)	MODERATE	Due to risk of bias
Clinical recurrence	645 (6 RCTs)	RR 0.50 (0.26 - 0.96)	37 per 1000 (5 -251)	182 per 1000 (26 - 1000)	179 per 1000 (69 -467)	273 per 1000 (107 - 698)	LOW	Due to risk of bias and imprecision
Severe endoscopic recurrence	463 (5 RCTs)	RR 0.41 (0.21 - 0.79)	49 per 1000 (13 – 185)	157 per 1000 (58 - 427)	114 per 1000 (48 – 271)	210 per 1000 (86 – 509)	MODERATE	Due to risk of bias

CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; TNF-α, tumor necrosis factor α.

* Endoscopic recurrence high risk: previous anti-TNFα exposure and/or penetrating disease

* Clinical recurrence high risk: previous anti-TNFα exposure, prior intestinal resection and/or non-stricturing non-penetrating disease (2 or more factors present)

* Severe endoscopic recurrence high risk: previous anti-TNFα exposure, prior intestinal resection and/or penetrating disease (2 or more factors present)

Discussion

Prophylactic medication for prevention of postoperative recurrence in CD is preferably tailored on individual risk stratification. Results of this meta-analysis of IPD show an overall advantage of postoperative anti-TNF-α prophylaxis as compared with thiopurines, both for prevention of endoscopic and clinical recurrence. Regression analysis revealed no additional risk factors associated with a different outcome of these prophylactic strategies.

Anti-TNF-α and thiopurine therapy are currently recommended as postoperative prophylactic strategies in international guidelines.[14,15] Our study shows that anti-TNF-α therapy was more effective in the prevention of postoperative endoscopic and clinical recurrence as compared with thiopurines in a large portion of postoperative CD patients. The observation of superiority of anti-TNF-α to thiopurines is supported by previously published network meta-analyses on this topic.[19,20,30-33] It should be noted that thiopurines are proven more effective than placebo in this setting. In addition, thiopurines carry evident advantages over anti-TNF-α with regard to costs and oral administration route. Therefore, a strategy with thiopurines including dose optimization (through therapeutic drug monitoring) would be an interesting strategy to enhance its prophylactic effect, and these data would add to current literature. Similarly, data on the combination of anti-TNF-α and thiopurines are scarce and require further exploration. In this meta-analysis of IPD, we were unable to include combination therapy because only 1 study provided data. In this study, endoscopic recurrence was observed in 4 (21%) of 19 patients within 1.5 years. Other data that are eagerly awaited are prospective randomized trials with other therapeutic CD agents (eg, vedolizumab and ustekinumab) in a postoperative setting.[14,15,34]

To our knowledge, this is the first study investigating the treatment effect of anti-TNF-α and thiopurines in different subgroups and risk groups at individual patient level. We found a significant difference in the risk of clinical recurrence for anti-TNF-α vs thiopurines between smokers and nonsmokers at the timing of surgery. However, we could not prove a differential effect of anti-TNF-α vs thiopurines in smokers vs nonsmokers for endoscopic recurrence. Furthermore, this finding should be interpreted with caution because it might be biased by the presence of confounding factors influencing clinical recurrence rates in smokers (eg, previous exposure to medication, disease behavior, prior intestinal resection). Unfortunately, the sample size not allowed further analysis to correct for these confounding factors. A possible beneficial effect of thiopurines in smokers for the prevention of clinical recurrence might be explained by the mechanism of action of thiopurines, via inhibition of T cell proliferation. A recent prospective study showed that active smoking postoperative CD patients have a lower diversity of the T cell repertoire and a higher percentage of clonal T cell expansions in mucosal biopsies of the resection specimen as compared with nonsmokers. An increased proportion of clonal expansions at the timing of ileocecal resection was also

associated with higher postoperative endoscopic recurrence rates.[35] Most importantly, smoking is an important individual risk factor for postoperative recurrence in previous observational studies as well as clinical trials, and patients who quit smoking have an improved postoperative prognosis.[9,36-38] Therefore, encouragement of smoking cessation in all preoperative CD patients is advised, before the decision to start postoperative prophylaxis.

Preferably, postoperative prophylactic treatment is restricted to patients at high risk of recurrence. In the present study, the risk reduction for endoscopic recurrence for anti-TNF-α vs thiopurine therapy was as high as 40% in high-risk patients vs 23% in low-risk patients; the difference in treatment effect was not statistically different. The interpretation of high- vs low-risk groups is hindered because of wide CIs and inconsistent results between clinical and endoscopic recurrence. Larger differences in absolute risk may be anticipated between both therapies if we would be able discriminate better between high- and low-risk patients.

Studies on prophylactic treatments are often performed in so-called high-risk populations with 1 or more of the following risk factors: smoking, penetrating disease, or prior intestinal resection. However, current evidence on these risk factors is still scarce and contradicting.[1,14,39,40] In the present study, previous anti-TNF-α exposure and penetrating disease behavior were associated with endoscopic recurrence. Previous anti-TNF-α exposure and prior intestinal resection were associated with clinical recurrence, whereas stricturing and penetrating disease behavior were found to be protective (with $P < .20$). Possibly this difference is explained by small population size or inconsistency in applied definitions, eg, if patients ever had penetrating disease vs penetrating disease as the indication for the current resection. These contradicting results affirm the unmet need for adequate clinical, histologic, serologic, or genetic predictors.

Meta-analysis of IPD data collection allowed standardization of the outcome definition for clinical and endoscopic recurrence, establishment of different risk groups and absolute risk differences for the different therapies, and finally, adjustment for differences in follow-up time, in a large population of postoperative CD patients collected from only randomized clinical trials. Nevertheless, some limitations of this study need to be taken into consideration. First, a larger study population might be necessary to find significant differences in subgroups and to find adequate markers for recurrence. Second, although we attempted to use uniform outcome measures for all studies, the definition of clinical recurrence included both CDAI and Harvey-Bradshaw Index, and cutoffs varied to some extent, as a CDAI score was unavailable for the study of Armuzzi et al[16] and baseline CDAI scores were not available for all studies. Finally, we performed a per-protocol analysis because reasons and dates of loss to follow-up were not available on participant level for all studies, because of which an intention-to-treat analysis could not be performed. This could have especially influenced the assessment of the outcome endoscopic recurrence, as the

per-protocol analysis excludes patients who did not undergo endoscopy because of early dropout caused by clinical or biochemical recurrence, adverse events, or if a patient did not want to undergo colonoscopy. To prevent underestimation of the event rate, a sensitivity analysis was performed with a combined clinical and/or endoscopic recurrence endpoint, which showed similar results as were reported in the Results.

In conclusion, postoperative prophylaxis with anti-TNF-α overall is superior to thiopurine therapy in the prevention of clinical and endoscopic recurrence in CD patients. No differences in treatment effect were found in different subgroups and risk groups. Additional predictors or biomarkers for postoperative clinical and endoscopic recurrence are necessary to develop individualized prophylactic strategies.

Acknowledgments

Raw data from this meta-analysis are not publicly available because the data belong to the original studies. Upon request, contact details of the data holders can be shared. Analytical methods can be shared upon reasonable request to the corresponding author.

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This study used data from the TOPPIC trial, obtained via the Edinburgh Clinical Trials Unit, situated in the University Court of the University of Edinburgh.

This study, carried out under YODA Project #2018-3236, used data obtained from the Yale University Open Data Access Project, which has an agreement with Janssen Research & Development. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or Janssen Research & Development.

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Supplementary data

Systematic Search

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('tumor necrosis factor inhibitor'/exp OR ('monoclonal antibody'/de AND 'tumor necrosis factor'/de) OR 'mercaptopurine'/exp OR '6 mercaptopurine derivative'/exp OR 'azathioprine'/exp OR 'tioguanine'/exp OR 'immunomodulating agent'/de OR 'immunologic factor'/de OR 'immunosuppressive agent'/de OR 'immunosuppressive treatment'/de OR (mercaptopurin* OR Thiopurin* OR tioguanin* OR thioguanin* OR azathioprin* OR immunomodulat* OR (immunolog* NEAR/3 factor*) OR immunosuppress* OR immuno-modulat* OR immuno-suppress* OR adalimumab* OR infliximab* OR ((tnf OR 'tumor necrosis factor') NEAR/3 (inhibitor* OR anti OR antagonist* OR block* OR antibod*))):kw,ab,ti) AND ('Crohn disease'/exp OR (Crohn*):kw,ab,ti) AND ('postoperative period'/de OR ('Crohn disease'/exp/dm_su AND ('recurrent disease'/de)) OR (postoperat* OR post-operat* OR postsurg* OR post-surg* OR surgical*-induc* OR after-surg* OR (recurr* NEAR/3 surg*)):kw,ab,ti)

Medline Ovid

(Tumor Necrosis Factor-alpha/ai OR (Antibodies, Monoclonal/ AND Tumor Necrosis Factor-alpha/) OR exp 6-Mercaptopurine/ OR Thioguanine/ OR Immunologic Factors/ OR Immunosuppressive Agents/ OR (mercaptopurin* OR Thiopurin* OR tioguanin* OR thioguanin* OR azathioprin* OR immunomodulat* OR (immunolog* ADJ3 factor*) OR immunosuppress* OR immuno-modulat* OR immuno-suppress* OR adalimumab* OR infliximab* OR ((tnf OR tumor necrosis factor) ADJ3 (inhibitor* OR anti OR antagonist* OR block* OR antibod*))).kw,ab,ti.) AND (Crohn Disease/ OR (Crohn*).kw,ab,ti.) AND (Postoperative Period/ OR (Crohn disease/su AND (Recurrence/)) OR (postoperat* OR post-operat* OR postsurg* OR post-surg* OR surgical*-induc* OR after-surg* OR (recurr* ADJ3 surg*)).kw,ab,ti.)

Cochrane CENTRAL

((mercaptopurin* OR Thiopurin* OR tioguanin* OR thioguanin* OR azathioprin* OR immunomodulat* OR (immunolog* NEAR/3 factor*) OR immunosuppress* OR immuno-modulat* OR immuno-suppress* OR adalimumab* OR infliximab* OR ((tnf OR 'tumor necrosis factor') NEAR/3 (inhibitor* OR anti OR antagonist* OR block* OR antibod*))):kw,ab,ti) AND ((Crohn*):kw,ab,ti) AND ((postoperat* OR post-operat* OR postsurg* OR post-surg* OR surgical*-induc* OR after-surg* OR (recurr* NEAR/3 surg*)):kw,ab,ti)

Web of Science

TS=(((mercaptopurin* OR Thiopurin* OR tioguanin* OR thioguanin* OR azathioprin* OR immunomodulat* OR (immunolog* NEAR/2 factor*) OR immunosuppress* OR immuno-modulat* OR immuno-suppress* OR adalimumab* OR infliximab* OR ((tnf OR "tumor necrosis factor") NEAR/2

(inhibitor* OR anti OR antagonist* OR block* OR antibod*)))) AND ((Crohn*)) AND ((postoperat* OR post-operat* OR postsurg* OR post-surg* OR surgical*-induc* OR after-surg* OR (recurr* NEAR/2 surg*))))

Google Scholar

mercaptopurin|Thiopurine|tioguanine|thioguanine|azathioprine|immunomodulating|"immunologic factors"|immunosuppressants|adalimumab|infliximab|"tnf inhibitors|antagonist|blockers|antibodies" Crohn postoperative|postsurgical|"after surgery"

Supplementary table 1. Characteristics of the excluded studies (due to unavailability of individual participant data)

	Country	Study medication	Total number of patients	Study period	Clinical recurrence definition	Endoscopic recurrence definition	Follow-up time
Hanauer et al. Gastroenterology, 2004[10]	USA, Belgium	MP	47	1992 - 1996	Clinical Recurrence Grading scale > 2	Rutgeerts ≥i2	104 weeks
		5ASA	44				
		Plac	40				
Herfarth et al. Gastroenterology, abstract, 2006[41]	Germany	AZA	18	NR	NR	NR	52 weeks
		5ASA	20				
Scapa et al. JCC, abstract, 2015[42]	Israel	ADA	11	NR	NR	Rutgeerts ≥i2	52 weeks
		MP	8				

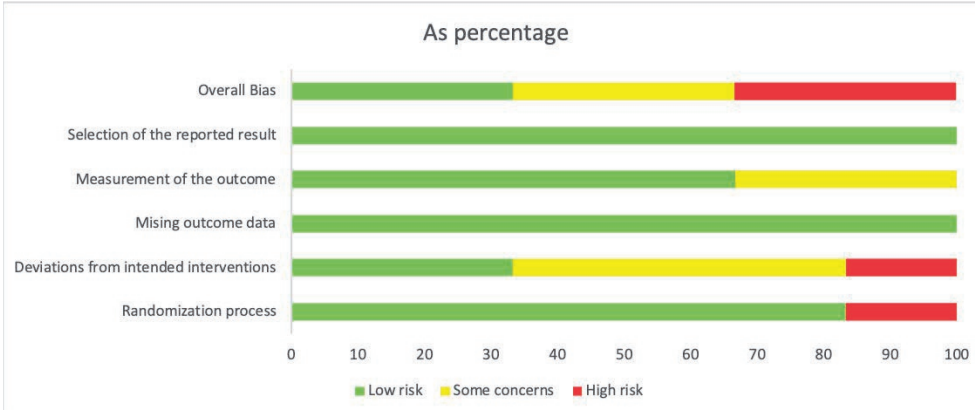
Supplementary table 2. Characteristics of included patients displayed per study

Study	Total N	Male gender N(%)	Age in yrs Median(IQR)	Disease duration in yrs Median(IQR)	Active smoking N(%)	Montreal A N(%)			Montreal L N(%)		Montreal B N(%)			Previous intestinal resection N(%)
						<17	17-40	>40	Ileum	Ileocolon	Luminal	Stricturing	Penetrating	
Ardizzone. 2004[29]	70	49(70)	38.0 (33.0 – 49.0)	-	28(40)	-	-	-	57(81)	4(6)	0(0)	32(46)	38(54)	38 (54)
Missing N(%)		0			0	76(100)			9(13)		0			0
Armuzzi. 2013[16]	21	15(71)	32.0 (22.0 – 37.0)	2.1 (1.0 – 5.0)	8(38)	2(10)	16(76)	3(14)	12(57)	9(43)	4(19)	6(29)	11(52)	5(24)
Missing N(%)		0			0	0			0		0			0
Lopéz-SanRoman. 2017[17]	65	31(48)	36.0 (31.0 – 43.0)	6.1 (2.4 – 10.8)	13(20)	1(2)	56(86)	8(12)	39(60)	26(40)	-	-	27(41)	4(6)
Missing N(%)		0			0	0			0		38(59)			0
Mowat. 2016[27]	233	91(39)	38.0 (28.0 – 49.0)	1.8 (0.5 – 8.3)	48(21)	13(6)	171(74)	48(21)	93(39)	140(58)	92(40)	106(46)	34(14)	71(30)
Missing N(%)		0			24(10)	1(0)			0		1(0)			0
Regueiro. 2013[28]	205	106(52)	24.0 (26.0 – 45.0)	1.4 (0.3 – 6.5)	57(29)	5(4)	85(73)	26(22)	90(45)	112(55)	15(7)	42(21)	145(72)	74(36)
Missing N(%)		0			1(0)	89(43)			3(1)		1(0)			1(0)
Savarino. 2013[26]	51	24(47)	49.0 (37.0 – 56.0)	6.0 (3.0 – 13.0)	19(37)	0(0)	28(55)	23(45)	25(49)	26(51)	0(0)	13(25)	38(75)	51(100)
Missing N(%)		0			0	0					0			0

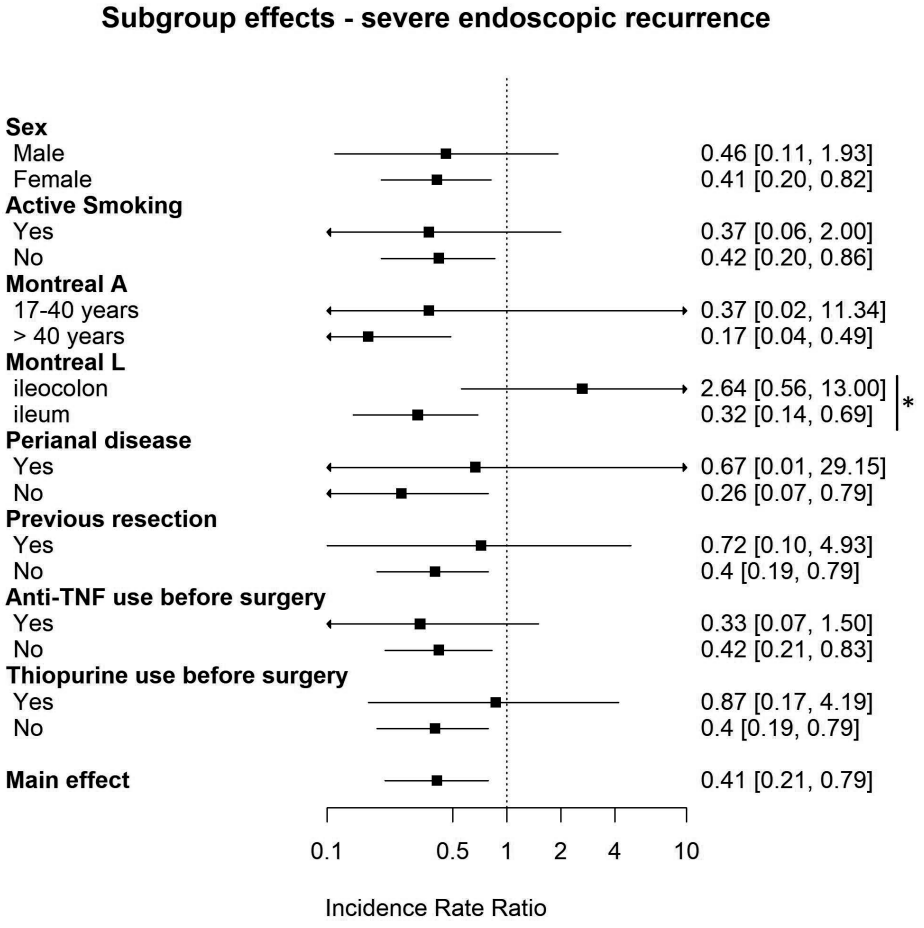
Supplementary table 3. Baseline characteristics of the study population displayed per type study medication

		Anti-TNFα N=166	Thiopurines N=208	5-ASA N=58	Placebo N=213
Male sex, N (%)		79 (47.6)	98 (47.1)	38 (65.5)	101 (47.4)
Age in years, median (IQR)		35.5 (28.0 – 45.0)	38.0 (30.0 – 49.0)	43.0 (33.0 – 58.0)	35.0 (25.0 – 46.0)
Active smoking, N(%)		52 (31.5)	51 (25.5)	24 (41.3)	46 (23.4)
	Missing	*1*	*8*	*0*	*16*
Disease duration in years, median (IQR)		4.6 (1.0 – 8.8)	2.9 (0.7 – 8.2)	4.5 (3.0 – 11.0)	1.3 (0.3 – 7.7)
	Missing, N	*49*	*59*	*40*	*67*
Montreal A, N (%)	< 17 years	2 (1.7)	8 (4.5)	0 (0)	11 (6.4)
	17-40 years	94 (80.3)	131 (73.6)	7 (38.9)	124 (72.1)
	> 40 years	21 (18.0)	39 (21.9)	11 (61.1)	37 (21.5)
	Missing, N	*49*	*30*	*40*	*41*
Montreal L, N (%)	Ileum	76 (46.3)	108 (53.5)	42 (76.4)	90 (42.5)
	Ileocolonic	88 (53.7)	94 (46.5)	13 (23.6)	122 (57.5)
	Missing, N	*2*	*6*	*3*	*1*
Montreal B, N (%)	Non-stricturing non-penetrating	10 (7.0)	50 (26.3)	0 (0)	51 (24.3)
	Stricturing	29 (19.9)	81 (42.6)	25 (43.1)	64 (30.5)
	Penetrating	106 (73.1)	59 (31.1)	33 (56.9)	95 (45.2)
	Missing, N	*21*	*18*	*0*	*3*
Previous surgery in medical history, N (%)		60 (36.4)	83 (39.9)	37 (63.8)	63 (29.6)
	Missing, N	*1*	*0*	*0*	*0*
Previous thiopurine use, N(%)		92 (55.4)	115 (55.3)	10 (17.2)	101 (47.4)
Previous anti-TNFα use, N(%)		59 (35.5)	41 (19.7)	1 (1.7)	39 (18.3)

Supplementary figure 1. Risk of bias assessment (Cochrane risk of bias tool for randomized clinical trials (ROB2))



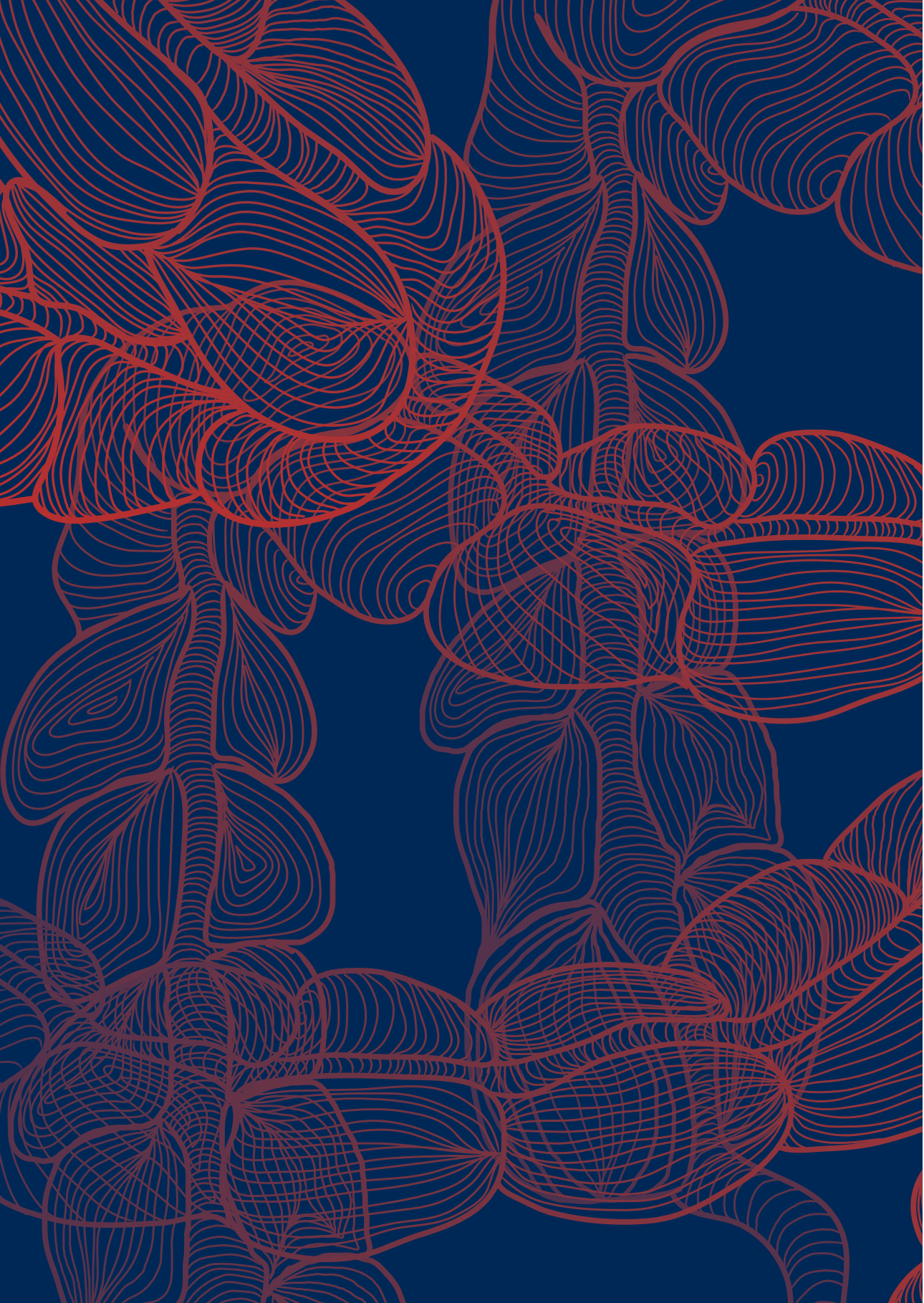
Supplementary figure 2. Network meta-analysis of anti-TNFα versus thiopurines in the prevention of postoperative recurrence in Crohn's disease, in different subgroups. Presented are Relative Risks and confidence intervals for severe endoscopic recurrence



* Significant subgroup effect

PART IV

Discussion



CHAPTER 10

Summary, discussion, future perspectives and general conclusion

Summary and discussion

The aim of this thesis is to enhance knowledge regarding postoperative recurrence after ileocolonic resection (ICR) in Crohn's Disease (CD) patients. In the first part of this thesis, we focused on epidemiology of intestinal resections and re-resections throughout the past decades. In addition, we assessed the risk of cholecystectomy after ileal resection. The second part described the postoperative disease course and prediction of postoperative recurrence, specifically the timing of ICR, isolated inflammation of the ileal blind loop and Paneth cell function. The third part of this thesis focused on the prevention of postoperative recurrence, with regards to a management strategy incorporating risk stratification and type of postoperative prophylactic medication. In this chapter, a summary of the thesis is provided including discussion and future perspectives.

Part I: Epidemiology

Pre and postoperative management paradigms for CD have changed over the past decades. In **chapter 2**, we investigated the impact of these changes on intestinal resection rates and re-resection risk between 1991 and 2015, in a nationwide cohort study in 8.170 patients with CD with long-term follow-up data from the Dutch nationwide pathology database PALGA. We demonstrated a substantial decrease in intestinal resection rate, corrected for the increase in CD prevalence, over the past decades in the Netherlands. This decrease was observed for all anatomic locations of resection, i.e. small bowel, ileocolonic, colonic and rectum. Furthermore, we found a decreasing trend in the risk of re-resection, with a 4 times lower hazard of re-resection in 2015 as compared to 1991. Previous reports on time trends in intestinal resections in CD have shown conflicting results.[1-6] However, large meta-analyses confirmed a marked decrease in resection rate over time, in line with our results.[7-9] A recent meta-analysis found a 10-year resection risk of 26% after 2000 as compared to 46% before 2000.[9] Although in our study we observed a decrease in intestinal resection and re-resection rate throughout the entire follow-up period, the most substantial decrease was found between 1991 and 1999. Possible factors contributing to the observed decreasing trend are earlier disease detection,[10] improved monitoring strategies, including easier access to endoscopy, new diagnostic tools e.g. Video Capsule Endoscopy (VCE) and fecal calprotectin, [11-13] and the introduction of thiopurines and anti-TNFα as medical therapy for CD.[14-17] It could be hypothesized that treatment with these new drug therapies has led to a change in the disease course of CD. Prevention of complicated disease might have led to fewer resections. However, whether the introduction of CD medication has led to a change in the natural course of CD is still a matter of debate.[5, 10] A large study by Murthy et al. using health administrative cost data from Ontario, Canada, aimed to evaluate the effect of the introduction of anti-TNFα on hospitalizations and resection rates in IBD patients.[18] This study, similarly to our data, found the strongest decrease in resection rate before the introduction of anti-TNFα and concluded that the introduction of anti-TNFα has not led to the expected

decrease in resection rates for CD. **Chapter 3** represents a letter that elaborates on this, as the depicted conclusion seems oversimplified. We concluded, more positively, that among two different epidemiological areas (Canada and the Netherlands) we observe a decrease in intestinal resection rates in CD, probably as a marker of improved prognosis, attributed to various aspects of the improvement of care in patients with CD. Several recent studies have attempted to investigate the relation between introduction of anti-TNFα agents and intestinal resection rates. One Canadian study found overall increasing surgery rates in patients with CD despite higher use of anti-TNFα agents.[19] However, a majority of recent reports described a decreasing trend in intestinal resections and re-resections in the biologic era, alongside the earlier and more widespread use of anti-TNFα.[20-25] Nevertheless, whether the decreasing trend in intestinal resections for CD can be directly attributed to anti-TNFα use remains controversial as it is influenced by multiple other factors e.g. fewer active smokers, earlier diagnosis and earlier immunosuppressant use. Therefore, quantification of the effect of (earlier) use of anti-TNFα on CD resection rates is difficult.

The postoperative disease course of patients with CD could be complicated by CD recurrence. Another long-term complication arising after ileal resection is the risk of gallstone formation. CD patients, especially patients with ileal disease or previous ileal resection, are at increased risk of gallstone formation.[26,27] In **chapter 4** we assessed the clinical relevance of this increased risk, by investigating the risk of cholecystectomy after ileal resection in patients with CD, using nationwide pathology data with long-term follow-up between 1991 and 2015. Our data showed an annual risk of cholecystectomy after ileal resection is 0.5% that increased almost linearly during follow-up to 10.5% after 20 years. In line with previous studies on the increased risk of gallstone formation, the risk of cholecystectomy in our postoperative CD population was 3 times higher as compared to the general pouplation.[26,27] Factors associated with cholecystectomy in our study included female sex and ileal re-resection. Although an increased risk of cholecystectomy in females is also described in the general population, previous studies in patients with CD reported no gender differences with regards to risk of gallstones.[27-30] Furthermore, a later year of ileal resection was associated with an increased risk of cholecystectomy. This could be explained by the global observation of increased gallstone prevalence and increased cholecystectomy rates in the general population.[31-36] Even though the risk of cholecystectomy in CD patients after ileal resection is higher as compared to healthy controls, the overall risk of cholecystectomy was low and does not seem to warrant synchronous prophylactic cholecystectomy during ileal resection in CD patients. Nevertheless, our data do justify increased alertness on gallstone disease in symptomatic patients with CD after ileal resection.

Part II: Prediction

Intestinal resection does not cure CD, and postoperative recurrence is common. Factors associated with postoperative recurrence have been widely studied, with variable results.[37-40]

Due to evolving CD medical treatment options, the choice of resection as therapeutic option might have been postponed and reserved for patients with severe complicated disease refractory to medical therapy. However, a landmark randomized controlled trial found that the outcome after ICR is comparable to step-up to anti-TNFα with regards to quality of life and cost-effectiveness.[41,42] Nevertheless, the outcome after early ICR rather than postponed ICR remains unclear. The first chapter of part II, **chapter 5**, describes a retrospective, multicenter cohort study including 822 patients with CD after primary ICR between 2000 and 2019. This study aimed to investigate risk factors for postoperative recurrence and assess the association between timing of ICR and postoperative prognosis, in a multivariable model. A large selection of covariates that could influence postoperative prognosis (e.g. smoking, age, Montreal classification, pre-operative and postoperative medication use) were included in the model. In multivariable regression analysis, ileocolonic disease localisation (compared to ileal disease location) and a more recent year of ICR were associated with an increased risk of endosocpic recurrence (defined as Rutgeerts' score ≥i2b during postoperative endoscopy or radiological evidence of disease activity within 18 months). Furthermore, postoperative prophylactic medication with an immunomodulator or in combination with a biological was protective of endoscopic recurrence, in agreement with current published meta-analyses.[43, 44] Active smoking is one of the strongest and consistent risk factors in current literature.[45] In our study, smoking was not associated with endoscopic recurrence but was associated with an increased risk of escalation of IBD medication and re-resection. With regards to the association between timing of ICR and postoperative prognosis, we conclude that patients with an indication for an ICR at or shortly after CD diagnosis had a beneficial postoperative disease course, illustrated by a 7% lower chance of escalation of IBD medication within 18 months and a 14% lower long-term re-resection risk. This is consistent with earlier published data.[46-48] Endoscopic recurrence rates were similar. For all other patients, short-term and long-term postoperative prognosis was comparable after early and late ICR, when corrected for covariates influencing the postoperative disease course. Therefore, we concluded that timing of ICR should not be weighed in clinical decisions regarding postoperative disease management.

Currently, the most performed anastomosis after ICR is an ileocolonic side-to-side anastomosis. Inflammation of the ileal blind loop, formed during side-to-side anastomosis, is not taken into account in the assessment of postoperative recurrence with the Rutgeerts' score.[49] Data on the clinical relevance of inflammation of the ileal blind loop are missing. In **Chapter 6,** we describe that isolated inflammation of the ileal blind loop during postoperative ileocolonoscopy in patients with CD after ICR seemed to be associated with symptoms and a worse prognosis characterized by a high risk of endoscopic recurrence in the neoterminal ileum and high risk of re-resection. The Rutgeerts' score was first described in 1990, when traditional end-to-end anastomosis was common.[49] Although side-to-side anastomosis is currently the preferred anastomosis, a majority of endoscopy reports did not contain a

description of the ileal blind loop. The etiology of ileal blind loop inflammation is unknown, and could be different from the etiology of lesions in the neoterminal ileum. Furthermore, it does not seem to be influenced by known risk factors for CD recurrence. Possible hypotheses for the etiology of ileal blind loop inflammation include ischemia, disturbance of the microbiome by fecal stasis and diversion ileitis.[50-52] Although the limitations of this study, inherent to its retrospective design, should be taken into account, we demonstrated that ileal blind loop inflammation seems to be associated with an unfavorable prognosis and that the ileal blind loop needs to be assessed during endoscopy in postoperative patients with CD, both in clinical practice and in prospective research. Recently, studies on Kono-S end-to-end anastomosis have shown promising results, with lower endoscopic recurrence rates compared to traditional anastomotic techniques.[53,54]

As prediction of the postoperative CD disease course with clinical risk factors remains challenging, recent studies have also focused on histologic risk factors. One of these potential histologic predictors is abnormal function of the Paneth cell. Paneth cells are specialized secretory cells in the small bowel, which are essential to gut homeostasis. They control microbial invasion in the intestine and help protect the barrier function by secreting antimicrobial proteins. Several studies have suggested a role for Paneth cells in CD pathology. [55-57] **Chapter 7** is focused on Paneth cell dysfunction in the resection specimen as predictor for re-resection. ICR specimen of CD patients were retrospectively reviewed and several aspects of Paneth cell function were assessed. We found that neither Paneth cell numbers, lysozyme expression levels nor distribution were associated with requirement of re-resection for CD. Genetic polymorphism affecting Paneth cell function, ER stress levels and levels of Faecalibacterium prausnitzii or adherent-invasive Escherichia Coli (AIEC) were also not predictive of re-resection. In contrast to our data, previous studies identified abnormal Paneth cell granule morphology, representing Paneth cell dysfunction, in the resection specimen as predictor of postoperative endoscopic CD recurrence.[58,59] Possibly, the negative outcome of our study can be explained by small population size and retrospective design without standardized follow-up schedule. Furthermore, the outcome measure re-resection rather than endoscopic recurrence might be explanatory for the contradictory results, although generally re-resection can be considered a robust outcome marker for postoperative prognosis. We conclude that our explorative study was unable to identify Paneth cell aberrations as either cause or marker for re-resection in CD patients. Nevertheless, previous studies on Paneth cell dysfunction in the ileocolonic resection specimen as predictor of postoperative recurrence showed promising results that certainly deserve further investigation.[58,59] Of note, the procedure of identifying granule morphology of Paneth cells as a biomarker can be difficult, due to sparse presence of abnormal phenotypes. Translation of this method to clinical practice could be troublesome, as assessment of large numbers of crypts per patient makes this a time consuming effort. Furthermore, the somewhat subjective nature of the analysis would require the need of

confirmation of observations by various pathologists. Possibly machine learning based techniques could improve feasibility of this technique.

Part III: Prevention

Current European and American guidelines propose to start medical prophylaxis after ICR in patients with CD at high risk of postoperative recurrence. Only general descriptions of high-risk patients exist. Most used clinical risk factors are smoking, penetrating disease and prior resection in medical history.[40,60-62] In our prospective observational cohort study, described in **chapter 8**, we incorporated a postoperative management algorithm where patients with one or more of these risk factors present would receive postoperative prophylaxis with a biological and/or immunomodulator. A total of 213 postoperative patients with CD (93 [43.7%] low-risk and 120 [56.3%] high-risk) were included. Adherence to the management algorithm was 65%. Omitting prophylaxis in high-risk patients resulted in significant increase of endoscopic recurrence of 23%. Furthermore, starting prophylaxis in patients considered low risk by the management algorithm reduced postoperative endoscopic recurrence with 29%. Our results emphasize the importance of postoperative prophylactic medication in high-risk patients, and the persistent need for adequate and strong predictors of recurrence, to be able to discriminate better between low and high-risk patients. Histologic risk factors may improve predictability of the postoperative disease course. Three histologic risk profiles were assessed. ROC curves for these clinical risk factors combined with three histological risk profiles were plotted. The following three histologic profiles were analyzed: a. adapted from the ECCO guideline[40] (presence of granulomas and/or myenteric plexitis), b. based on the meta-analysis from Tandon et al.[63] (presence of active inflammation of resection margins, granulomas and/or myenteric and/or submucosal plexitis), and c. based on a study by Hammoudi et al.[64] (transmural lesions). We found that addition of these risk profiles to known clinical risk factors led to slight improvement of predictive value, with the highest receiver operating statistic for clinical risk factors combined with risk factors by Tandon et al.[63] (Tandon combined with clinical risk factors AUC 0.73 vs clinical risk factors alone AUC 0.70). Therefore we conclude that prophylactic medication reduces the risk of endoscopic recurrence after ICR in both low-risk and high-risk patients with CD. Clinical risk stratification has an acceptable predictive value, which is slightly improved by adding histology.

Current guidelines advise to start thiopurines or anti-TNFα was postoperative prophylaxis in high-risk patients with CD. These guidelines express no preference for one of both therapies.[40,62] In **chapter 9** we used individual participant data of 645 patients from 6 randomized clinical trials, to demonstrate a superior effect of anti-TNFα compared to thiopurine prophylaxis for the prevention of endoscopic recurrence (Rutgeerts' score ≥i2), RR 0.52 (95%CI 0.33–0.80), clinical recurrence (CDAI >200 or HBI ≥8), RR 0.50 (95%CI 0.26–0.96), and severe endoscopic recurrence (Rutgeerts' score ≥i3), RR 0.41 (95%CI 0.21-0.79). This is consistent with published meta-analyses on this topic.[43, 44, 65] Nevertheless, thiopurines

were previously found to be superior to placebo.[66] Furthermore, thiopurine therapy carries evident advantages e.g. costs and oral administration route. Individual participant data collection allowed standardization of the outcome definition for endoscopic and clinical recurrence, establishment of different risk groups and absolute risk differences for the different therapies, and finally, adjustment for differences in follow-up time. In Poisson regression analysis, previous exposure to anti-TNFα and penetrating disease behaviour were associated with an increased risk of postoperative endoscopic recurrence. In high-risk patients, the absolute risk difference for endoscopic recurrence at 1 year after ICR for anti-TNFα vs thiopurines was as high as 40%. However, we found no evidence of a difference in treatment effect for anti-TNFα compared to thiopurines in high vs low-risk groups. The identification of stronger, more accurate predictors or biomarkers for postoperative endoscopic and clinical recurrence would improve the development of individualized prophylactic treatment strategies.

Future perspectives

The explanation for the observed declining rate of intestinal resections in CD warrants further investigation, since these factors may drive a further improvement in CD prognosis. Important questions to answer are whether the use of biologicals has led to a change in the disease course, and whether early use of biologicals could lead to avoidance of intestinal resection and re-resection. Furthermore, the influence of other strategies e.g. strict monitoring, patient education and smoking cessation, are largely unknown.

Future opportunities to improve CD prognosis after intestinal resection include (a combination of) standardized preoperative optimization of the physical and psychological status of patients, advancement of surgical techniques, improved postoperative (non-invasive) monitoring of disease activity, and (new) prophylactic medication tailored to patients at high risk of CD recurrence.

Prehabilitation before surgery, by improvement of the nutritional status and physical and psychological condition of the patient, could improve postoperative outcomes in patients with CD. Previous studies demonstrated that prehabilitation of colorectal cancer patients prior to abdominal surgery reduced hospital stay.[67, 68] In patients with CD, preoperative improvement of the nutritional status may improve the body composition.[69] However, data on the effect of specific prehabilitation programs on postoperative outcomes in patients with CD (e.g. complication rates and postoperative recurrence) are lacking.

With regards to surgical techniques, implementation of the Kono-S anti-mesenteric end-to-end anastomosis has shown promising results, with lower endoscopic recurrence rates

as compared to traditional anastomotic techniques.[53,70,71] However, larger, high quality, prospective studies are necessary to confirm this advantage, before this technique could be routinely used in clinical practice. One of the hypotheses for the improved outcome after Kono-S anastomosis is the anti-mesenteric anastomosis. Another report showed that inclusion of the mesentery in ICR would reduce postoperative surgical recurrence.[72] Therefore, further study into the role of the mesentery in postoperative CD recurrence would be of interest.

To evaluate the course of CD after intestinal resection, reliable markers of prognosis are required, and may include non-invasive options. Promising results were published for ultrasonography in the diagnosis of postoperative CD recurrence, with a high sensitivity and specificity, and a good correlation to endoscopy. If combined with contrast-enhanced ultrasonography, it could further improve the diagnosis of severe recurrence.[73-76] In addition, fecal calprotectin could be implemented as a non-invasive, surrogate marker of endoscopic recurrence, thereby deferring postoperative endoscopy in a selection of patients.[77-80] Yet, larger prospective studies comparing standardized postoperative follow-up with fecal calprotectin to follow-up with ileocolonoscopy are lacking. Endoscopy is still considered the gold standard in the diagnosis of postoperative recurrence. However, the definition of endoscopic recurrence requires further investigation. Although the Rutgeerts' score is widely used in research and clinical practice to quantify postoperative endoscopic recurrence, a few concerns hamper its validity. First of all, the association with long-term prognosis is unclear, as the score was never prospectively validated. The prognosis of anastomotic lesions vs lesions in the (neo)terminal ileum is still a matter of debate. Furthermore, the prognostic value of the Rutgeerts' score after re-resections is unknown. Prospective validation and further assessment of the cut-off for endoscopic recurrence, to obtain an accurate marker of CD prognosis, would significantly add to current literature. Secondly, although a recent study demonstrated a substantial inter and intraobserver reliability of the Rutgeerts score, assessed by expert endoscopists, other studies reported moderate or low reliability.[81-83] Especially differentiation between scores i1, i2a and i2b proved to be difficult, which could lead to inconsistency in therapeutic decisions.[82-84] Perhaps a more specific definition of these scores or a separate description of the observed ileal and anastomotic lesions could further improve inter and intraobserver reliability. In addition, future implementation of artificial intelligence approaches might be a future solution for this.

We have shown that anti-TNFα agents are superior to thiopurines in the prevention of postoperative recurrence. However, a study assessing a strategy with thiopurines including dose optimization would be interesting. Furthermore, combination therapy with thiopurines could hypothetically improve anti-TNFα pharmacokinetics, although previous studies did not show an advantage of combination therapy over anti-TNF monotherapy in inducing CD remission.[85-87] A knowledge gap exists with regards to the efficacy of combination therapy

in the prevention of postoperative CD recurrence. Moreover, prospective randomized trials investigating the efficacy of vedolizumab and ustekinumab for the prevention of postoperative recurrence would add to current literature. In addition, although we found no difference in treatment effect between anti-TNF and thiopurines in high and low-risk groups, enhancement of postoperative risk stratification could allow further research into personalized postoperative treatment strategies.

Furthermore, data from this thesis demonstrated that postoperative prophylactic medication significantly reduces (early) postoperative endoscopic recurrence. However, the long-term prognosis of patients receiving prophylactic medication as compared to endoscopy-guided medical therapy is unknown. Randomized controlled studies comparing long-term outcome for these postoperative strategies are needed.

Postoperative risk stratification is challenging, as prediction of the postoperative disease course of CD is difficult. CD has a multifactorial etiology and varying disease course, which complicates the identification of predictors that can be used in a large patient population. Available clinical predictors have appeared to be unsatisfactory in our and previous studies. Some new determinants have shown promising results; firstly, diversity of the T-cell population in the ICR specimen, defined as a larger number of clonal T-cell expansions, was significantly associated with active smoking and postoperative recurrence.[88] Secondly, impaired Paneth cell phenotypes in the ileal resection specimen were found to be associated with postoperative recurrence.[58,59] Although we could not demonstrate a role for Paneth cell dysfunction in the prediction of re-resection, the data of these previous studies warrant future investigation. Thirdly, the composition of ileal mucosa-associated microbiota at the time of ICR could predict postoperative recurrence, although no consistent specific microbiota were identified and quantification of the corresponding risk of recurrence is not available, hampering translation to clinical practice.[89,90] Finally, an altered body composition, characterized by sarcopenia and increased visceral fat, was previously shown to be associated with disease severity, adverse outcomes and increased endoscopic recurrence.[91-95] However, more evidence is necessary before these factors can be incorporated in postoperative risk stratification in clinical practice.

General conclusion

Although resection rates have decreased over time, ICR is an important modality of CD treatment. The decision wether to perform intestinal resection in patients with CD requires a patient-specific, multidisciplinary approach. CD has a varying postoperative disease course, which is difficult to predict. Current available clinical and histologic risk factors have an acceptable predictive value for postoperative endoscopic recurrence. More

accurate predictors are necessary to enhance postoperative risk stratification. Postoperative prophylaxis significantly reduces the risk of postoperative recurrence and should be prescribed in high-risk patients. Refinement of risk stratification could help establish personalized postoperative treatment strategies, thereby reducing postoperative recurrence in high-risk patients and reducing unnecessary long-term exposure to medication in low-risk patients.

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PART V

Appendices

Nederlandse samenvatting

De ziekte van Crohn (CD) is een chronische inflammatoire darmziekte (IBD), gekenmerkt door een ziektebeloop met afwisselende periodes van opvlamming en remissie. CD kan overal in het maagdarmkanaal voorkomen, maar manifesteert zich meestal in het ileum en het colon.[1] De etiologie van CD is niet geheel bekend. De meest ondersteunde hypothese is dat CD voortkomt uit een combinatie van meerdere factoren, bijv. omgevingsfactoren, genetische predispositie en microbiële veranderingen, die bijdragen aan ontregeling van de immuunrespons en resulteren in een zichzelf in stand houdende ontsteking van het darmslijmvlies.[1,2] CD heeft vaak een progressief natuurlijk beloop, waarbij intestinale transmurale ontsteking leidt tot ziektecomplicaties, waaronder stricturen en penetrerende complicaties (fistel of abces).[1, 3] Een groot deel van de patiënten met CD zal tijdens het ziekteverloop een darmresectie ondergaan. De meest uitgevoerde darmresectie is een ileocoecaal of ileocolische resectie (ICR). Chirurgische resectie van het aangetaste darmsegment kan zorgen voor snelle vermindering van symptomen, maar het is geen curatieve therapie voor CD, en een recidief van actieve darmontsteking na ICR komt frequent voor. In de literatuur wordt een postoperatief recidief van actieve CD vaak onderverdeeld in klinisch (symptomen veroorzaakt door actieve inflammatie), endoscopisch (endoscopisch bewijs van actieve inflammatie) en chirurgisch recidief (re-resectie).[4]

Chirurgische resectie vormt een belangrijk onderdeel van de interdisciplinaire behandeling van CD. De postoperatieve behandeling van CD is complex, aangezien een postoperatief recidief frequent voorkomt en het percentage re-resecties hoog is. Er bestaat een kennishiaat met betrekking tot postoperatieve risicostratificatie en de optimale behandelstrategie. Het doel van dit proefschrift is om de kennis op het gebied van postoperatieve recidief van actieve CD na darmresectie te vergroten.

In het eerste deel van dit proefschrift bespreken we de epidemiologie van darmresecties en re-resecties gedurende de afgelopen decennia. Daarnaast wordt het risico op cholecystectomie na ileum resectie besproken. Het tweede deel beschrijft risicofactoren voor postoperatief recidief van CD, met name de timing van ileocolische resectie, ontsteking van de blinde lis van het ileum en dysfunctie van Paneth cellen in het ileum. Het derde deel van dit proefschrift is gericht op de preventie van postoperatief recidief, met betrekking tot een managementstrategie gebaseerd op risicostratificatie en de soort postoperatieve profylactische medicatie. In dit hoofdstuk vatten we deze onderdelen samen en worden suggesties voor toekomstig onderzoek besproken.

Deel I: Epidemiologie

Pre- en postoperatieve behandelstrategieën voor CD zijn de afgelopen decennia sterk veranderd. In **hoofdstuk 2** hebben we de impact van deze veranderingen op het aantal

darmresecties en het risico op re-resectie tussen 1991 en 2015 onderzocht in een landelijke cohortstudie van 8.170 patiënten met CD met lange termijn follow-up uit de landelijke pathologiedatabase PALGA. Hierbij hebben we een substantiële afname van het aantal darmresecties in Nederland gedurende de afgelopen decennia aangetoond, gecorrigeerd voor de toename van prevalentie van CD in deze periode. Deze afname in aantal resecties werd geobserveerd voor alle typen resecties, namelijk dunne darm, ileocolisch, colon en rectum. Verder rapporteerden we een dalende trend van het risico op re-resectie, met een 4 keer lager risico op re-resectie in 2015 in vergelijking met 1991. Hoewel we in onze studie een afname in darmresecties observeerden gedurende de gehele follow-up periode, vond de meest substantiële afname plaats tussen 1991 en 1999. Mogelijke factoren die bijdragen aan de waargenomen dalende trend in resecties zijn vroegere ziektedetectie,[5] verbeterde monitoringstrategieën, waaronder makkelijkere toegang tot endoscopie, nieuwe diagnostische hulpmiddelen, bijv. Videocapsule-endoscopie (VCE) en fecaal calprotectine,[6-8] en de introductie van thiopurines en anti-TNFα als medicamenteuze therapie voor CD.[9-12] Verondersteld zou kunnen worden dat behandeling middels deze nieuwe medicamenteuze therapieën geleid heeft tot een verandering van het natuurlijke ziekteverloop van CD. Hierbij zou het voorkómen van gecompliceerde ziekte met medicatie geleid kunnen hebben tot minder resecties. Of de introductie van medicamenteuze therapieën voor CD daadwerkelijk heeft geleid tot een verandering in het natuurlijke beloop van CD is echter nog een punt van discussie.[5, 13]

Een grote studie door Murthy et al. waarbij gebruik gemaakt is van data van administratieve kosten van gezondheidszorg in Ontario, Canada, had als doel het effect van de introductie van anti-TNFα op ziekenhuisopnames en resectiepercentages patiënten met IBD te evalueren.[14] Deze studie vond, vergelijkbaar met onze data, de sterkste afname van het aantal resecties vóór de introductie van anti-TNFα en concludeert dat de introductie van anti-TNFα niet heeft geleid tot de verwachte afname van resecties voor CD. **Hoofdstuk 3** beschrijft een kort commentaar op dit artikel, aangezien de weergegeven conclusie te eenvoudig lijkt. Wij concludeerden, vanuit een meer positief oogpunt, dat we in twee verschillende epidemiologische gebieden (Canada en Nederland) een afname van het aantal darmresecties voor CD waarnemen, waarschijnlijk als marker voor een verbeterde prognose, toegeschreven aan verschillende aspecten van de verbetering van de zorg voor patiënten met CD.

Het postoperatieve ziekteverloop van patiënten met CD kan worden gecompliceerd door een recidief van actieve CD. Een andere complicatie op de lange termijn die optreedt na ileum resectie is het risico op galsteenvorming. Patiënten met CD, met name patiënten met ziekte gelokaliseerd in het ileum of een eerdere ileum resectie, hebben een verhoogd risico op galsteenvorming.[15, 16] In **hoofdstuk 4** werd de klinische relevantie van dit verhoogde risico beoordeeld, door het risico op cholecystectomie na ileum resectie bij patiënten met

CD te onderzoeken, met behulp van landelijke pathologie data met langdurige follow-up tussen 1991 en 2015. Het jaarlijkse risico op cholecystectomie na ileumresectie was 0,5%, en nam tijdens de follow-up periode bijna lineair toe tot 10,5% na 20 jaar. Het risico op cholecystectomie in onze postoperatieve CD populatie was 3 keer hoger in vergelijking met de algemene populatie. Factoren geassocieerd met cholecystectomie in onze studie waren vrouwelijk geslacht en eerdere ileum resectie. Verder was een later jaar van ileum resectie geassocieerd met een verhoogd risico op cholecystectomie. Dit zou kunnen worden verklaard door de wereldwijde observatie van een verhoogde prevalentie van galstenen en verhoogde cholecystectomie percentages in de algemene bevolking.[17-22] Hoewel het risico op cholecystectomie bij CD patiënten na ileum resectie hoger is in vergelijking met gezonde controles, was het algehele risico op cholecystectomie laag en lijkt dit geen profylactische cholecystectomie gelijktijdig met een ileum resectie bij patiënten met CD te rechtvaardigen. Desalniettemin rechtvaardigen onze data wel een verhoogde alertheid op galstenen bij symptomatische patiënten met CD na ileum resectie.

Deel II: Voorspellen

Ten gevolge van de ontwikkeling van nieuwe behandelingsopties voor CD, wordt de keuze voor resectie als therapie mogelijk uitgesteld en voorbehouden voor patiënten met een ernstige gecompliceerde ziekte die ongevoelig zijn voor medicamenteuze therapie. Een belangrijke gerandomiseerde studie bevestigde echter dat het succes van ICR vergelijkbaar is met het succes van step-up behandeling met anti-TNFα op het gebied van kwaliteit van leven en kosteneffectiviteit.[23, 24] Echter, de prognose na ICR vroeg in het ziektebeloop ten opzichte van een uitgestelde ICR is onduidelijk. Het eerste hoofdstuk van deel II, **hoofdstuk 5**, beschrijft een retrospectieve, multicenter cohortstudie met 822 patiënten met CD na primaire ICR tussen 2000 en 2019. Deze studie had als doel risicofactoren voor postoperatief recidief te onderzoeken en de associatie tussen timing van ICR en postoperatieve prognose te beoordelen, in een multivariabel model. Een grote selectie van co variabelen die de postoperatieve prognose zouden kunnen beïnvloeden (bijv. roken, leeftijd, Montreal-classificatie, preoperatief en postoperatief medicatiegebruik) werd in dit model meegenomen. In multivariabele regressieanalyse waren ileocolische lokalisatie van CD (in vergelijking met ileum lokalisatie) en een recenter jaar van ICR geassocieerd met een verhoogd risico op endoscopisch recidief (gedefinieerd als Rutgeerts' score ≥i2b tijdens postoperatieve endoscopie of radiologisch bewijs van ziekteactiviteit binnen 18 maanden na ICR). Bovendien was postoperatieve profylactische behandeling met een immunomodulator alleen, of in combinatie met een biological, beschermend voor een endoscopisch recidief.[25, 26] Met betrekking tot de associatie tussen timing van ICR en postoperatieve prognose, concluderen we dat patiënten met een indicatie voor een ICR op het moment van -of kort na- CD diagnose een gunstig postoperatief ziekteverloop hadden, geïllustreerd door een 7% lagere kans op escalatie van IBD medicatie binnen 18 maanden en 14% lager risico op re-resectie op lange termijn. Er was geen verschil in percentage endoscopisch recidief. Voor alle

andere patiënten was de postoperatieve prognose op korte en lange termijn vergelijkbaar na vroege en late ICR, gecorrigeerd voor co variabelen die het postoperatieve ziekteverloop beïnvloeden. Derhalve concludeerden we dat de timing van ICR niet dient te worden meegewogen in klinische beslissingen met betrekking tot de postoperatieve behandeling van CD.

Op dit moment is de meest gebruikte methode van anastomose na ICR een ileocolische side-to-side anastomose. Inflammatie van de blinde ileum lis, gevormd tijdens side-to-side anastomose, wordt niet meegenomen bij de beoordeling van postoperatief recidief middels de Rutgeerts'score.[27] Data met betrekking tot de klinische relevantie van inflammatie van de blinde ileum lis ontbreken. In **hoofdstuk 6** wordt geschreven dat geïsoleerde inflammatie van de blinde lis tijdens postoperatieve ileocolonoscopie bij patiënten met CD na ICR geassocieerd was met symptomen en een slechtere prognose, gekenmerkt door een hoog risico op endoscopisch recidief in het neoterminale ileum en een hoog risico op re-resectie. De etiologie van blinde lis inflammatie is onbekend en verschilt mogelijk van de etiologie van laesies in het neoterminale ileum. Bovendien lijkt het niet te worden beïnvloed door bekende risicofactoren voor CD recidief. Mogelijke hypothesen voor de etiologie van inflammatie van de blinde ileum lis zijn ischemie, verstoring van het microbioom door fecale stase en diversion ileitis.[28-30] Hoewel de beperkingen van deze studie, inherent aan het retrospectieve ontwerp, in ogenschouw dienen te worden genomen, hebben we aangetoond dat blinde ileum lis inflammatie geassocieerd lijkt te zijn met een ongunstige prognose en dat de blinde lis dient te worden beoordeeld tijdens endoscopie bij postoperatieve patiënten met CD.

Gezien het postoperatieve ziekteverloop van CD moeilijk te voorspellen is met behulp van klinische risicofactoren, hebben recente studies zich ook gericht op histologische risicofactoren. Een van deze mogelijke histologische voorspellers is een abnormale functie van de Paneth cel. Paneth cellen zijn gespecialiseerde secretoire cellen in de dunne darm, die essentieel zijn voor de homeostase van de darm. Ze controleren de invasie van microben in de darm en helpen de barrièrefunctie te beschermen door antimicrobiële eiwitten (o.a. lysozymen) uit te scheiden. Verschillende studies hebben gesuggereerd dat Paneth-cellen een rol spelen bij de pathofysiologie van CD.[31-33] **Hoofdstuk 7** is gericht op Paneth cel dysfunctie in het resectiepreparaat als voorspeller voor re-resectie. ICR preparaten van CD patiënten werden retrospectief geanalyseerd waarbij verschillende aspecten van de Paneth cel functie werden beoordeeld. In onze studie waren noch Paneth cel aantallen, expressie niveaus van lysozymen noch de distributie van lysozymen geassocieerd met re-resectie voor CD. Ook genetische polymorfismen die de functie van Paneth cellen beïnvloeden, ER-stress niveaus en aanwezigheid van de microbiota Faecalibacterium prausnitzii of adherent-invasive Escherichia Coli (AIEC) waren niet voorspellend voor re-resectie. Mogelijk kan de negatieve uitkomst van onze studie worden verklaard door een kleine populatiegrootte en de retrospectieve studie opzet met afwezigheid van een gestandaardiseerd follow-up

schema. Bovendien kan de uitkomstmaat re-resectie in plaats van endoscopisch recidief verklarend zijn voor de tegenstrijdige resultaten, hoewel over het algemeen re-resectie kan worden beschouwd als een robuuste marker voor postoperatieve prognose. We concluderen dat onze exploratieve studie niet in staat was om abnormale Paneth cellen te identificeren als voorspeller voor re-resectie bij patiënten met CD. Belangrijk is om te vermelden dat de procedure voor het identificeren van abnormale morfologie van Paneth cellen als biomarker moeilijk kan zijn vanwege de schaarse aanwezigheid van abnormale fenotypes. De vertaling van deze methode naar de klinische praktijk kan complex zijn, omdat de beoordeling van grote aantallen crypten per patiënt dit een tijdrovende bezigheid maakt. Bovendien zou het enigszins subjectieve karakter van de analyse de bevestiging van observaties door verschillende pathologen vereisen. Mogelijk zijn op machine learning gebaseerde benaderingen hiervoor een toekomstige oplossing.

Deel III: Voorkomen

De huidige Europese en Amerikaanse richtlijnen adviseren om medicamenteuze profylaxe te starten na ICR bij patiënten met CD met een hoog risico op postoperatief recidief. Er bestaan alleen algemene beschrijvingen van hoog-risico patiënten. De meest gebruikte klinische risicofactoren zijn roken, penetrerende ziekte en eerdere resectie in de medische voorgeschiedenis.[34-37] In een prospectieve observationele cohortstudie, beschreven in **hoofdstuk 8**, werd gebruik gemaakt van een postoperatief behandel algoritme waarbij bij patiënten met aanwezigheid van een of meer van deze risicofactoren gestart werd met postoperatieve profylaxe middels een biological en/of immunomodulator. In totaal werden 213 postoperatieve CD patiënten (93 [43,7%] laag risico en 120 [56,3%] hoog risico) geïncludeerd. Het postoperatieve behandel algoritme werd in 65% van de gevallen gevolgd. Het nalaten van starten van profylaxe bij hoog-risico patiënten resulteerde in een significante toename van endoscopisch recidief van 23%. Bovendien verminderde het starten van profylaxe bij patiënten die volgens het algoritme als laag risico werden beschouwd, het postoperatieve endoscopische recidief met 29%. Deze resultaten benadrukken het belang van postoperatieve profylactische medicatie bij hoog-risico patiënten, en de persisterende behoefte aan adequate en sterke voorspellers van recidief, om beter onderscheid te kunnen maken tussen laag- en hoog-risico patiënten. Mogelijk kunnen histologische risicofactoren de voorspelbaarheid van het postoperatieve ziekteverloop verbeteren. Toevoeging van histologische risicoprofielen aan bekende klinische risicofactoren leidde tot een lichte verbetering van de voorspellende waarde, met de hoogste receiver operating statistiek voor klinische risicofactoren gecombineerd met risicofactoren door Tandon et al.[38] (Tandon in combinatie met klinische risicofactoren AUC 0,73 vs. alleen klinische risicofactoren AUC 0,70). Wij concluderen in deze studie dat profylactische medicatie het risico op endoscopisch CD recidief na ICR vermindert bij zowel laag- als hoog-risico patiënten met CD. Klinische risicostratificatie heeft een acceptabele voorspellende waarde, die enigszins wordt verbeterd na het toevoegen van histologische factoren.

De huidige richtlijnen adviseren om te starten met thiopurines of anti-TNFα als postoperatieve profylaxe in hoog-risico patiënten met CD. In deze richtlijnen wordt geen voorkeur gegeven aan een van beide therapieën.[36, 37] **Hoofdstuk 9** beschrijft een studie waarbij gebruikt werd gemaakt van individuele patiënten data van 645 deelnemers aan 6 gerandomiseerde klinische trials. Deze studie toont een superieur effect van anti-TNFα aan in vergelijking met thiopurine profylaxe voor de preventie van endoscopisch recidief (Rutgeerts' score ≥i2), RR 0,52 (95%CI 0,33-0,80), klinisch recidief (CDAI >200 of HBI ≥8), RR 0,50 (95%CI 0,26-0,96), en ernstig endoscopisch recidief (Rutgeerts-score ≥i3), RR 0,41 (95% BI 0,21-0,79). Het verzamelen van individuele patiëntgegevens in deze studie maakte het mogelijk om de uitkomstdefinitie voor endoscopisch en klinisch recidief te standaardiseren, verschillende risicogroepen en absolute risicoverschillen voor de verschillende therapieën te analyseren, en ten slotte, een correctie toe te passen voor de verschillen in follow-up tijd. Bij Poisson regressieanalyse was eerdere blootstelling aan anti-TNFα en penetrerend ziektegedrag geassocieerd met een verhoogd risico op postoperatief endoscopisch CD recidief. Bij hoog-risico patiënten was het absolute risicoverschil voor endoscopisch recidief 1 jaar na ICR voor anti-TNFα versus thiopurines 40%. We vonden echter geen bewijs voor een verschil in behandeleffect voor anti-TNFα in vergelijking met thiopurines in hoog- vs. laag-risico groepen. De identificatie van sterkere, nauwkeurigere voorspellers voor postoperatief endoscopisch en klinisch recidief zou de ontwikkeling van geïndividualiseerde profylactische behandelingsstrategieën kunnen verbeteren.

Aanbevelingen voor toekomstig onderzoek

De verklaring voor het waargenomen afnemende aantal darmresecties bij CD verdient nader onderzoek, aangezien deze factoren de prognose van CD verder zouden kunnen verbeteren. Toekomstige mogelijkheden om de prognose van CD na darmresectie te verbeteren zijn onder meer (een combinatie van) gestandaardiseerde preoperatieve optimalisatie van de fysieke en psychologische gesteldheid van patiënten, verbetering van chirurgische technieken, verbeterde postoperatieve (niet-invasieve) monitoring van ziekteactiviteit en (nieuwe) profylactische medicatie afgestemd op patiënten met een hoog risico op CD recidief.

Prehabilitatie voorafgaand aan de operatie, door verbetering van de voedingsstatus, psychologische en fysieke conditie van de patiënt, zou de postoperatieve uitkomsten van CD patiënten kunnen verbeteren. Viscerale adipositas is geassocieerd met ernstigere CD activiteit en bleek een individuele voorspeller te zijn van postoperatief endoscopisch recidief.[39-43] Een prehabilitatieprogramma gericht op preoperatieve patiënten met CD zou de postoperatieve uitkomsten kunnen verbeteren, bijv. met lagere kans op complicaties en

kleiner risico op postoperatief recidief.[44, 45] Er is echter meer bewijs nodig om het effect van specifieke prehabilitatieprogramma's op postoperatieve uitkomsten aan te tonen.

Met betrekking tot chirurgische technieken heeft de nieuwere Kono-S anti-mesenteriale end-to-end anastomose veelbelovende resultaten laten zien, met lagere endoscopische recidief percentages in vergelijking met traditionele anastomotische technieken.[46-48] Er zijn echter grotere prospectieve studies van hoge kwaliteit nodig om dit voordeel te bevestigen, voordat deze techniek routinematig in de klinische praktijk kan worden toegepast. Een van de hypothesen voor de verbeterde uitkomst na Kono-S anastomose is de anti-mesenteriale aard van de anastomose. Een eerdere studie toonde aan dat het meenemen van het mesenterium bij ICR de kans op re-resectie zou verminderen.[49] Derhalve zou verder onderzoek naar de rol van het mesenterium in postoperatieve recidief van CD interessant zijn.

Om het verloop van CD na ICR te evalueren, zijn betrouwbare markers voor de prognose vereist, welke ook niet-invasieve opties kunnen omvatten. Veelbelovende resultaten zijn gepubliceerd met betrekking tot echografie bij de diagnose van postoperatief CD recidief, met een hoge sensitiviteit en specificiteit en een goede correlatie met endoscopie. Combinatie met contrast-echografie zou de diagnose van ernstig recidief verder kunnen verbeteren.[50-53] Verder zou fecaal calprotectine kunnen worden geïmplementeerd als een niet-invasieve marker voor endoscopisch recidief, waardoor postoperatieve endoscopie bij een selectie van patiënte vermeden kan worden.[54-57] Grotere prospectieve studies die gestandaardiseerde postoperatieve follow-up middels fecaal calprotectine vergelijken met follow-up middels ileocolonoscopie ontbreken echter. Endoscopie wordt tot op heden beschouwd als de gouden standaard bij de diagnose van postoperatief CD recidief. De definitie van endoscopisch recidief vereist echter nader onderzoek. Hoewel de Rutgeerts score veel wordt gebruikt in zowel onderzoek als klinische praktijk om postoperatief endoscopisch recidief te kwantificeren, belemmeren een paar nadelen de validiteit van deze score. Allereerst is de associatie met de lange termijn prognose onduidelijk, aangezien de score nooit prospectief is gevalideerd. De prognose van anastomotische laesies versus laesies in het (neo)terminale ileum is nog altijd een punt van discussie. Verder is de prognostische waarde van de Rutgeerts score na re-resecties onbekend. Prospectieve validatie en verder onderzoek naar de afkapwaarde voor endoscopisch recidief, om zo een nauwkeurige marker van prognose van CD te verkrijgen, zou een significante toevoeging zijn aan de huidige literatuur. Ten tweede, hoewel een recente studie een substantiële inter- en intraobserver betrouwbaarheid van de Rutgeerts score door deskundige endoscopisten aantoonde, rapporteerden andere studies een matige of lage betrouwbaarheid.[58-60] Vooral differentiatie tussen scores i1, i2a en i2b bleek moeilijk, wat zou kunnen leiden tot inconsistentie in therapeutische beslissingen.[59-61] Mogelijk zou een meer specifieke definitie van deze scores of een aparte beschrijving van de waargenomen ileum- vs. de anastomotische laesies

de inter- en intraobserver betrouwbaarheid kunnen verbeteren. Tevens zou artificiële intelligentie in de toekomst een mogelijke oplossing kunnen bieden.

Anti-TNFα therapie is superieur aan thiopurine therapie bij het voorkomen van postoperatief recidief. Echter, een studie waarin een strategie met thiopurines inclusief dosisoptimalisatie wordt beoordeeld, zou van toegevoegde waarde zijn. Bovendien zou combinatie therapie met thiopurines de farmacokinetiek van anti-TNFα kunnen verbeteren, hoewel eerdere onderzoeken geen voordeel hebben aangetoond van combinatietherapie ten opzichte van anti-TNF monotherapie bij het induceren van CD remissie.[62-64] Er bestaat een kennishiaat met betrekking tot de werkzaamheid van combinatietherapie bij het voorkomen van postoperatief recidief van CD. Tevens zouden prospectieve gerandomiseerde onderzoeken naar de werkzaamheid van vedolizumab en ustekinumab voor de preventie van postoperatief recidief een aanvulling zijn op de huidige literatuur. Bovendien, hoewel geen verschil in behandelingseffect werd gevonden tussen anti-TNFα en thiopurines in hoog- en laag-risico groepen, zou verbetering van de postoperatieve risicostratificatie verder onderzoek naar gepersonaliseerde postoperatieve behandelingsstrategieën mogelijk maken.

Voorts toonde de data afkomstig uit dit proefschrift aan dat postoperatieve profylactische medicatie de kans op een (vroeg) postoperatief endoscopisch recidief significant vermindert. De lange termijn prognose van patiënten behandeld middels postoperatieve profylactische medicatie in vergelijking met een meer afwachtend beleid middels endoscopie-geleide medicamenteuze therapie is echter niet bekend. Er zijn gerandomiseerde gecontroleerde studies nodig die de lange termijn resultaten voor deze postoperatieve strategieën vergelijken.

Postoperatieve risicostratificatie vormt een uitdaging aangezien voorspelling van het postoperatieve ziekteverloop van CD complex is. CD heeft een multifactoriële etiologie en een wisselend ziekteverloop, hetgeen de identificatie van voorspellers die in een grote patiëntenpopulatie kunnen worden toegepast, bemoeilijkt. Beschikbare klinische voorspellers zijn in zowel onze als eerdere studies onvoldoende gebleken. Enkele mogelijke voorspellers hebben veelbelovende resultaten laten zien; Ten eerste was afname van de diversiteit van de T-cel populatie in het ICR preparaat, gedefinieerd als een groter aantal klonale T-celexpansies, significant geassocieerd met actief roken en postoperatief recidief. (65). Ten tweede bleken abnormale Paneth cel fenotypes in het resectie preparaat geassocieerd te zijn met postoperatief recidief.[66, 67] Hoewel wij geen rol voor Paneth cel dysfunctie hebben kunnen aantonen voor het voorspellen van re-resectie, rechtvaardigen de data van deze eerdere studies wel toekomstig onderzoek. Ten derde bleek de samenstelling van ileum mucosa-geassocieerde microbiota op het moment van ICR voorspellend voor postoperatief recidief, hoewel er geen consistente specifieke microbiota werden geïdentificeerd en kwantificering van het overeenkomstige risico op recidief niet beschikbaar is, hetgeen de

vertaling naar de klinische praktijk belemmert.[68, 69] Ten slotte werd eerder aangetoond dat een veranderde lichaamscompositie, gekenmerkt door sarcopenie en verhoogd visceraal vet, geassocieerd is met de ernst van de ziekte, nadelige uitkomsten en een verhoogde kans op endoscopisch recidief.[39-43] Er is echter meer bewijs nodig voordat deze factoren kunnen worden opgenomen in postoperatieve risicostratificatie in de klinische praktijk.

Conclusies

ICR is een belangrijk onderdeel van de behandeling van CD. De beslissing om over te gaan tot het uitvoeren van een resectie bij patiënten met CD vereist een patiënt specifieke, multidisciplinaire benadering. CD heeft een wisselend postoperatief ziekteverloop dat moeilijk te voorspellen is. De huidige beschikbare klinische en histologische risicofactoren hebben een acceptabele voorspellende waarde voor postoperatief endoscopisch recidief. Er zijn nauwkeurigere voorspellers nodig om de postoperatieve risicostratificatie te verbeteren. Postoperatieve profylaxe vermindert het risico op postoperatief recidief en dient te worden voorgeschreven bij patiënten met een hoog risico. Verbetering van de risicostratificatie zou kunnen helpen bij het opstellen van gepersonaliseerde postoperatieve behandelingsstrategieën, waardoor de kans op postoperatief recidief bij patiënten met een hoog risico wordt verminderd en onnodige langdurige blootstelling aan medicatie bij patiënten met een laag risico wordt voorkomen.

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Abbreviations

5-ASA	5-aminosalicylic acid
ADA	adalimumab
AGA	American Gastroenterological Association
APC	annual percentage change
AUC	area under the curve
AZA	azathioprine
BIC	Bayesian information criterion
BMI	body mass index
CBS	statistics Netherlands
CD	Crohn's disease
CDAI	Crohn's disease actvitiy index
CI	confidence interval
cm	centimeter
CT	computed tomography
d	day
DNA	deoxyribonucleic acid
ECCO	European Crohn's and Colitis Organization
ER	endoscopic recurrence
ER-stress	Endoplasmic reticulum stress
FFPE	formalin fixed paraffin embedded
FU	follow-up
g	gram
GI	gastrointestinal
HBI	Harvey bradshaw index
HR	hazard ratio
IBD	inflammatory bowel diseases
IBLI	ileal blind loop inflammation
ICC	Dutch initiative on Crohn's and Colitis
ICR	ileocolonic/ileocecal resection
IFX	infliximab
IQR	interquartile range
IR	ileal resection
kg	kilogram
mg	milligram
mo	month
MP	mercaptopurine
MRI	magnetic resonance imaging
N	number
OR	odds ratio
PALGA	Dutch nationwide population-based pathology database
PCR	polymerase chain reaction

plac	placebo
Q1	1st quartile
Q3	3rd quartile
RCT	randomized controlled trial
RF	risk factors
ROC	receiver operating characteristics
RR	relative risk
SNOMED	systematized nomenclature of medicine
TNF	tumor necrosis factor
VCE	video capsule endoscopy
w	week
yr	year

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Bibliography

Manuscripts related to this thesis

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   Decreasing trends in intestinal resection and re-resection in Crohn's disease: a nationwide cohort study
   Annals of Surgery. 2021 March; 273(3): 557-563

3. Evelien M.J. Beelen, C. Janneke van der Woude, Annemarie C. de Vries
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   Gut. 2020 September; 69(9): 1

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   Isolated ileal blind loop inflammation after intestinal resection with ileocolonic anastomosis in Crohn's disease: an often neglected endoscopic finding with an unfavorable outcome
   European Journal of Gastroenterology and Hepatology. 2019 November; 31(11): 1370-1375

5. Evelien M. J. Beelen*, Jorn C. Goet*, Katharina E. Biermann, Annette H. Gijsbers, W. Rudolph Schouten, C. Janneke van der Woude, Annemarie C. de Vries
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6. Evelien M.J. Beelen, Suk Y. Lam, Gwenny M. Fuhler, W. Rudolph Schouten, Maikel P. Peppelenbosch, C. Janneke van der Woude, Annemarie C. de Vries
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Indications, postoperative management, and long-term prognosis of Crohn's disease after ileocecal resection: a multicentre study comparing the East and West
Inflammatory Bowel Diseases. 2021 December; 30; izab316

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Journal of Gastroenterology and Hepatology 2020 November; 35(11):1902-1908

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Basic Introduction on SPSS, Molecular medicine postgraduate school, Erasmus MC, Rotterdam	2017
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Integrity in scientific research, department of Medical Ethics and Philosophy, Erasmus MC, Rotterdam	2017

Oral presentations

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Cholecystectomy risk in Crohn's disease patients after ileal resection: a long-term nationwide cohort study. Nederlandse Vereniging voor Gastro-enterologie voorjaarscongres, Veldhoven, the Netherlands	2018
Medicatie keuze na ileocoecaal resectie. ICC dag, Amsterdam, the Netherlands	2019
Postoperatieve terugkeer van M.Crohn na ileocolische resectie: voorspellen en voorkomen, regionale IBD avond, Ridderkerk, the Netherlands	2021

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Time trends in ileocecal resections and postoperative recurrence in Crohn's disease. Digestive Disease Week, Chicago, United States of America	2017
Isolated ileal blind loop inflammation after ileocolonic resection in Crohn's disease: an often neglected diagnosis with an unfavorable prognosis. 13th congress of European Crohn's and Colitis Organisation, Vienna, Austria	2018

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Cholecystectomy risk in Crohn's disease patients after ileal resection: a long-term nationwide cohort study. Digestive Disease Week, Washington D.C., United States of America	2018
Thiopurines versus anti-TNFα for the prevention of postoperative recurrence in Crohn's disease – meta-analysis. Digestive Disease Week, Washington D.C., United States of America	2018
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