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Disease Outcome of Ulcerative Colitis in an Era of Changing Treatment Strategies: Results from the Dutch Population-Based IBDSL Cohort

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Abstract

Background and Aims: In the past decades, treatment options and strategies for ulcerative colitis [UC] have radically changed. Whether these developments have altered the disease outcome at population level is yet unknown. Therefore, we evaluated the disease outcome of UC over the past two decades in the South-Limburg area of The Netherlands.

Methods: In the Dutch population-based IBDSL cohort, three time cohorts were defined: cohort 1991–1997 [cohort A], cohort 1998–2005 [cohort B], and cohort 2006–2010 [cohort C]. The colectomy and hospitalisation rates were compared between cohorts by Kaplan-Meier survival analyses. Hazard ratios [HR] for early colectomy [within 6 months after diagnosis], late colectomy [beyond 6 months after diagnosis], and hospitalisation were calculated using Cox regression models.

Results: In total, 476 UC patients were included in cohort A, 587 patients in cohort B, and 598 patients in cohort C. Over time, an increase in the use of immunomodulators [8.1%, 22.8% and 21.7%, respectively, $p < 0.01$] and biological agents [0%, 4.3% and 10.6%, respectively, $p < 0.01$] was observed. The early colectomy rate decreased from 1.5% in cohort A to 0.5% in cohort B [HR 0.14; 95% confidence interval 0.04–0.47], with no further decrease in cohort C [0.3%, HR 0.98; 95% confidence interval 0.20–4.85]. Late colectomy rate remained unchanged over time [4.0% vs 5.2% vs 3.6%, respectively, $p = 0.54$]. Hospitalisation rate was also similar among cohorts [22.3% vs 19.5% vs 18.3%, respectively, $p = 0.10$].

Conclusion: Over the past two decades, a reduction in early colectomy rate was observed, with no further reduction in the most recent era. Late colectomy rate and hospitalisation rate remained unchanged over time.

Keywords: Ulcerative colitis, epidemiology, surgery

1. Introduction

Ulcerative colitis [UC] is an invalidating, chronic inflammatory disease restricted to the colon. The disease course of UC is heterogeneous, ranging from long-term quiescent disease to fulminant, therapy-refractory disease necessitating rescue surgery. Population-based cohort studies report that 8–24% of UC patients ultimately need a colectomy, the majority within 2 years after diagnosis.[1,2,3,4,5,6,7] Colectomy with or without ileal pouch-anal reconstruction [IPAA] is an effective treatment for UC, but perioperative complications are frequently encountered.[8] Postoperatively, the procedure is associated with lower fecundity, pouchitis, and a decreased quality of life due to invalidating complaints such as frequent stools, urgency, and soiling.[9,10] Therefore, prevention of colectomy is an important goal in UC management.

In the past decades, treatment strategies for UC have changed. Immunomodulators are more frequently used and are given earlier in UC disease course nowadays.[11,12,13] In 2006, the therapeutic armamentarium extended with the registration of biological therapy for UC in The Netherlands. Both immunomodulators[14,15,16,17] and anti-tumour necrosis factor alpha [TNFα] agents[18,19,20] are effective in inducing and maintaining clinical remission in UC. In addition, follow-up data from the Active Ulcerative Colitis Trials (ACT) showed a lower colectomy rate in the infliximab [IFX] group [10%] compared with the placebo group [17%] at Week 54 in a trial population.[21] Recently, a decline in the annual colectomy rate was observed in a Canadian cohort after the year of registration of IFX, suggesting an effect of biological availability on UC disease outcome.[22] For immunomodulators, only an association between early use and a decreased risk of surgery was found in Crohn's disease.[23,24] Data in UC on this topic are lacking. Despite the well-described efficacy of current treatment modalities in trial populations, little is known about the real-life disease outcome of UC patients diagnosed in the current era, in which early use of immunomodulators is incorporated in guidelines and biological therapy is available.

The aim of this study was to evaluate the disease outcome of UC patients diagnosed in the current era at population level, and to gain insight into the evolution of the colectomy and hospitalisation rates over time.

2. Methods

2.1. Cohort description

The IBD South-Limburg [IBDSL] cohort is a well-characterised population-based inflammatory bowel disease [IBD] cohort in the South-Limburg area of The Netherlands.[25] Previous studies reported on the incidence of IBD in this area.[26,27] South-Limburg is a well-defined geographical entity located in the south-east of The Netherlands. It is bordered by Germany and Belgium in the east and south-west, and its northern border with the central part of The Netherlands is narrow. Between 1991 and 2010, the average population in South-Limburg was approximately 635 000.[28] Migration in and out of the area is low, with a net migration rate of 2.1 per 1000 inhabitants per year.[28] The area comprises two general hospitals [Atrium Medical Centre in Heerlen and Orbis Medical Centre in Sittard] and one academic referral hospital (Maastricht University Medical Centre [MUMC+] in Maastricht) providing almost all endoscopic gastroenterological services in the area.

From 1991, incident adult IBD patients diagnosed in the South-Limburg area are registered in IBDSL. Newly-diagnosed IBD patients are identified via hospital administration, diagnosis-treatment-combination codes [Dutch variant of the case-mix reimbursement system applied in several other countries[29]], and by a search in the nationwide digital pathology database [PALGA]. These registrations are reviewed based on the assumption that in-hospital diagnostics [endoscopy or imaging] are needed to establish IBD diagnosis. To assure its population-based character and its completeness, the IBDSL registry has been cross-checked with IBD patients present in patient registries from local GPs. This check indicated that 93% of all eligible IBD patients living in the South-Limburg area are actually included in the IBDSL cohort.[25] This study was approved for all centres by the Medical Ethics Committee of the Maastricht University Medical Centre [NL31636.068.10] and registered in ClinicalTrial.gov [NCT02130349].

2.2. Study population and design

All UC patients diagnosed between January 1, 1991 and December 31, 2010 were eligible for inclusion in the present study. Exclusion criteria were an age at diagnosis under 18 years, living outside South-Limburg, and a previous diagnosis of Crohn's disease [CD], unclassified colitis [IBD-U], or indeterminate colitis [IBD-I]. Demographic data, disease extent, medication use, and the dates of hospitalisation and colectomy were retrieved from medical records, using standardised registration forms.

To assess changes in the colectomy and hospitalisation rates, three time cohorts were composed, based on date of diagnosis: cohort 1991–1997 [cohort A], cohort 1998–2005 [cohort B], and cohort 2006–2010 [cohort C]. The latter cohort reflects the biological era, as the first anti-TNFα agent registered for UC [IFX] was available in The Netherlands as from 2006. The prebiological era was equally divided into two time periods. Patients were followed until last visit, date of migration out of the area, death, or end of data collection [December 31, 2011], whichever came first.

2.3. Definitions

The diagnosis of UC was based on the combination of clinical, endoscopic, or radiological findings in conjunction with histological findings as described by Lennard-Jones.[30] The date of the first endoscopy with typical mucosal inflammation was used as date of diagnosis. Disease location at diagnosis was classified as ulcerative proctitis [E1], left-sided UC [E2], and extensive UC [E3].[31] Use of steroids was defined as the use of any systemic corticosteroid orally or intravenously administered. Under this definition, budesonide was not considered systemic steroid treatment. Thiopurines comprised azathioprine, 6-mercaptopurine, and tioguanine. These agents were available during the complete time period of the present cohort and were gradually adopted in UC management in the 1990s. Thiopurines have been used in UC patients with steroid-dependent disease as well as in patients treated with ciclosporin for acute severe colitis. The 2008 and 2012 European guidelines[32,33] and 2009 Dutch guidelines[34] on UC management have been advocated in The Netherlands ever since their availability. According to these guidelines, anti-TNFα therapy is indicated in patients with moderately active UC refractory or intolerant to thiopurines, patients with moderately active steroid-refractory UC, and in patients with acute severe colitis failing intravenous corticosteroids [rescue therapy]. Acute severe disease and chronic active disease [steroid-dependent or steroid-refractory] were defined according to the criteria from the European Crohn's and Colitis Organisation.[35] Rescue therapy was defined as the administration of ciclosporin or IFX in patients with an acute severe colitis failing intravenous corticosteroids.

2.4. Outcome measures

Outcome measures of this study were medication use, occurrence of hospitalisation, and occurrence of colectomy. Colectomy was defined as colectomy with ileostomy, proctocolectomy with ileostomy, or colectomy with IPAA. If colectomy was performed within 6 months after diagnosis, we considered it as 'early colectomy'; operation beyond 6 months after diagnosis was considered to be 'late colectomy'. Hospitalisation was defined as a hospital admission due to UC-related complaints [first presentation or flare], UC-related surgery, or a combination of both. Short hospital admissions for IFX infusions or clinical colonoscopies only were excluded.

2.5. Statistical analyses

Data were presented as median with interquartile ranges [IQR], or as mean with standard deviation [SD], depending on normality of the underlying distribution. Continuous data were compared by an independent Student's t-test or a Kruskal-Wallis test in case of non-parametric data. Dichotomous data were compared by chi-square tests. A Kaplan-Meier survival analysis was used to estimate the cumulative proportion of patients who used immunomodulators or anti-TNFα agents, underwent colectomy, or were hospitalised 1, 2, and 5 years following diagnosis, so that differences in follow-up between patients were taken into account. Differences between groups were assessed by log-rank test [presented are the corresponding *p*-values] and by Cox regression analyses. A multivariable Cox regression model was used to compare medication use and the colectomy and hospitalisation rates between the three time cohorts. Disease extent at diagnosis, sex, and age at diagnosis were also included in the multivariable model, to adjust for possible confounding due to differences in disease prognosis or baseline characteristics between groups. Differences in hazards between groups were presented as hazard ratios [HR] with 95% confidence intervals [CI]. Two separate Cox models were created: one model to assess colectomy risk from date of diagnosis to 6 months after diagnosis [ie early colectomy] and another model to assess colectomy risk beyond 6 months after diagnosis [ie late colectomy], because the proportional hazards assumption was violated, indicating that the hazard ratio of colectomy was dependent on disease duration. One model estimating colectomy risk for the total follow-up period would have led to an underestimation of the early colectomy risk and an overestimation of the late colectomy risk.[36] All statistical analyses were performed using SPSS Version 21 [SPSS, Chicago, IL, USA] for Windows.

3. Results

3.1. Study population

From January 1991 to December 2010, 1661 patients were diagnosed with UC in South-Limburg, of whom 492 [29.6%] were in the MUMC+, 700 [42.1%] in the Atrium Medical Centre, and 469 [28.2%] in the Orbis Medical Centre.

In total, 1661 UC patients were analysed; 476 patients were diagnosed between 1991 and 1997 [cohort A], 587 patients between 1998 and 2005 [cohort B], and 598 patients between 2006 and 2010 [cohort C]. Median disease durations were 17.5 [IQR 15.5–19.3], 9.5 [IQR 7.6–11.5], and 3.3 [IQR 2.0–4.7] years, respectively. The main characteristics of the patients are outlined in Table 1.

3.2. Medication use

Thiopurines were frequently used by patients in all cohorts, but an increase in the number of patients on thiopurine treatment was observed between cohorts [Figure 1A]. The cumulative 5-year probability of using thiopurines was 8.1% in cohort A, 22.8% in cohort B, and 21.7% in cohort C. In contrast to the first cohort, a 2.2-fold increase in thiopurine use was observed in the second [adjusted HR 2.15; 95% CI 1.65–2.80] and a 2.4-fold increase in the third cohort [adjusted HR 2.38; 95% CI 1.73–3.26]. Between the two more recent cohorts, no significant difference was observed in the proportion of thiopurine users [adjusted HR 1.11; 95% CI 0.85–1.44]. Over time, a difference in the timing of initiating thiopurine treatment was also observed. Within a follow-up of 5 years, time to first prescription of thiopurine medication gradually reduced from a median of 23.3 months [IQR 12.9 – 38.6] in cohort A to a median of 16.9 months [IQR 7.5–36.5] in cohort B, to a median of 10.2 months [IQR 3.1 – 26.3] in cohort C, $p < 0.01$. Within the pre-defined time window of early colectomy [between diagnosis and 6 months thereafter], 0.9%, 4.7%, and 6.4% of all UC patients were already on thiopurine treatment in the three consecutive time cohorts, respectively.

Anti-TNFα therapy was registered in The Netherlands in 2006, so that biological therapy was available as from diagnosis only in the last cohort. The cumulative 5-year probability of using anti-TNFα

Table 1. Main characteristics of UC patients in the Dutch IBDSL cohort.

		Cohort A 1991–1997 [n = 476]	Cohort B 1998–2005 [*n* = 587]	Cohort C 2006–2010 [*n* = 598]	*p*-Value
Age at diagnosis	mean in years ± SD	43.0 ± 15.8	45.6 ± 16.3	48.2 ± 17.4	<0.01
Sex, male	*N* [%]	265 [55.7]	323 [55.0]	297 [49.7]	0.09
Disease location at diagnosis[a]					<0.01
E1: proctitis	*N* [%]	142 [30.5]	189 [32.3]	232 [38.8]	
E2: left-sided disease	*N* [%]	251 [54.0]	289 [49.4]	249 [41.6]	
E3: extensive disease	*N* [%]	72 [15.5]	107 [18.3]	117 [19.6]	
Follow-up	median in years [IQR]	17.5 [15.5–19.3]	9.5 [7.6–11.5]	3.3 [2.0–4.7]	<0.01
Medication ever used[b]					
mesalazine	*N* [%]	453 [98.9]	573 [97.8]	577 [96.5]	0.04
steroids	*N* [%]	237 [51.7]	276 [47.1]	395 [66.1]	<0.01
immunomodulators	*N* [%]	36 [8.1]	131 [22.8]	98 [21.7]	<0.01
ciclosporin	*N* [%]	18 [3.9]	20 [3.4]	1 [0.2]	<0.01
anti-TNFα	*N* [%]	0 [0]	25 [4.4]	52 [10.6]	<0.01

SD, standard deviation; IQR, interquartile range; UC, ulcerative colitis; TNF, tumour necrosis factor.

[a]Disease location at diagnosis could not be retrieved in 13 cases.

[b]Medication ever used was determined at 5-year follow-up.

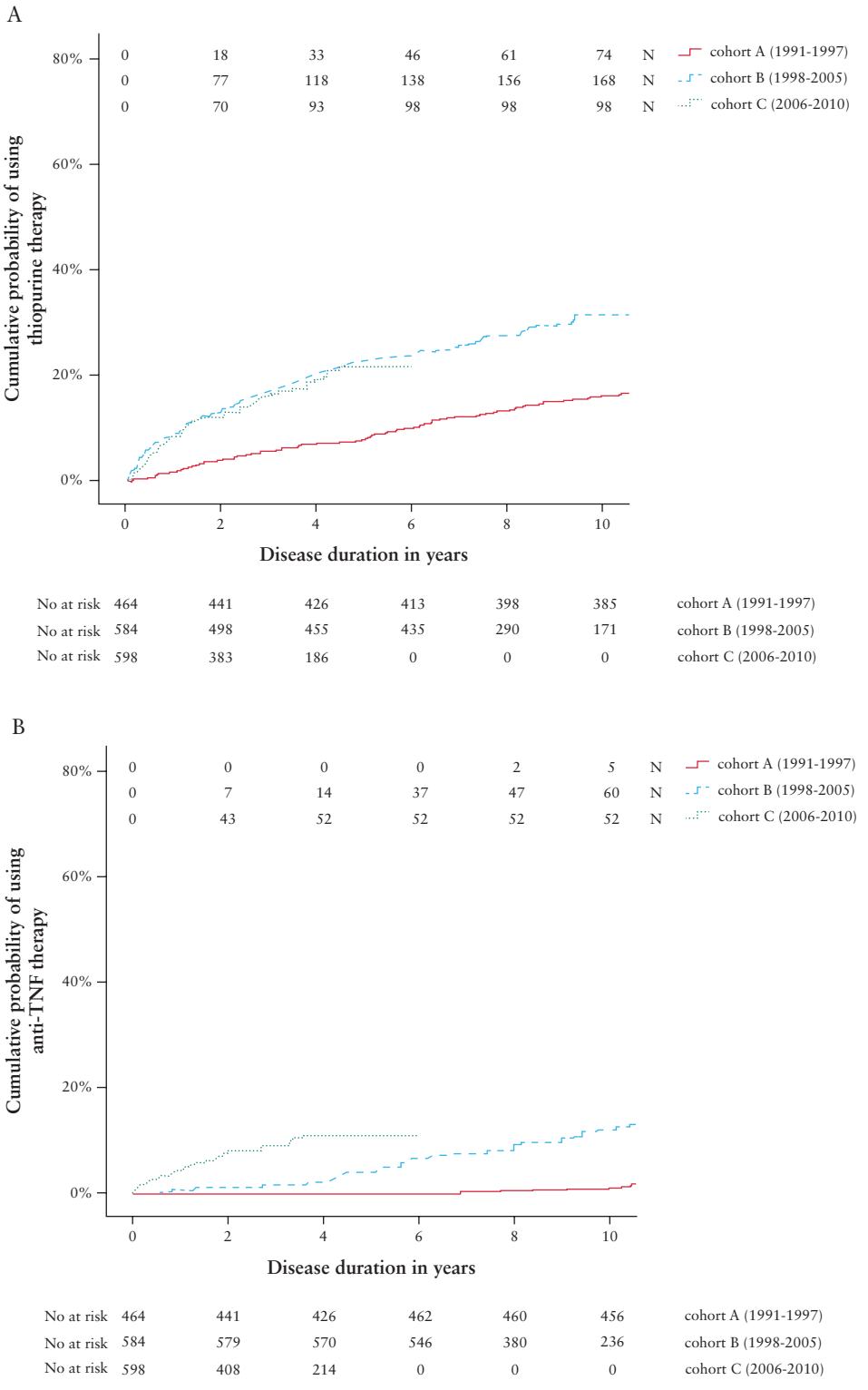

Figure 1. [A] Cumulative use of thiopurines in UC patients from the three cohorts. [B] Cumulative use of anti-TNFα agents in UC patients from the three cohorts. UC, ulcerative colitis; TNF, tumour necrosis factor.

therapy increased from 0% in cohort A to 4.3% in cohort B, to 10.6% in cohort C [Figure 1B]. The median time from diagnosis to first IFX infusion was 44.0 months [IQR 20.9–52.1] in the second and 12.2 months [IQR 3.9–22.3] in the most recent cohort, $p<0.01$. The majority of patients in cohort C who underwent colectomy had failed IFX therapy [72.2%]. Anti-TNFα use within 6 months after diagnosis was uncommon; no patient from cohort B and only 2.7% of the patients from cohort C used biological therapy early in their disease course. The majority of patients [79.2%] on anti-TNFα treatment had previously used thiopurine treatment. Combination therapy of anti-TNFα and a thiopurine was initially given to 29 patients [37.7%], but the thiopurine was discontinued during follow-up in

16 patients [55.2%], in 56.3% of these due to adverse effects and in 43.7% to quiescent disease.

Rescue therapy was prescribed in 21 patients from cohort A, 28 patients from cohort B, and 13 patients from cohort C. Corresponding 5-year cumulative probability rates of receiving rescue therapy were 1.7%, 3.1%, and 4.1%, respectively. Within the time window of early colectomy, no difference in the prevalence of rescue therapy was observed between the first two cohorts: 0.9% [$n = 6$] vs 1.0% [$n = 6$], $p = 0.68$, whereas no rescue therapy was used within 6 months in the most recent cohort. Ciclosporin was the common drug for rescue therapy before the availability of IFX, as it was given in 81.0% and 67.9% of the indicated cases in cohorts A and B, respectively. After registration of IFX, this anti-TNFα agent was most commonly used as rescue treatment in our area, reflected by the fact that all but one patient were given IFX as rescue therapy in cohort C.

3.3. Colectomy

The cumulative colectomy rate for all three cohorts is shown in Figure 2. In cohort A, 51 patients underwent colectomy and the cumulative probability of undergoing colectomy after 1, 2, and 5 years was 4.1%, 5.6%, and 7.5%, respectively. In cohort B, 43 patients underwent colectomy and the accompanying cumulative colectomy rate was 0.9%, 2.1%, and 5.7%, respectively. In the most recent cohort, 18 patients underwent colectomy and the accompanying cumulative colectomy rate in this cohort was 1.0%, 2.8%, and 4.1% after 1, 2, and 5 years, respectively. The indications for colectomy did not differ between cohorts [$p = 0.90$] and are shown in Table 2.

Analyses were performed separately for early colectomy [ie within 6 months after diagnosis] and late colectomy [ie colectomy beyond 6 months after diagnosis] and results are shown in Table 3. In total, 23 patients underwent early colectomy, 17 patients from the first, 3 from the second, and 3 from the third cohort. Over time, a decrease in the number of early colectomies was observed. The early colectomy rate attenuated from 1.5% in the first to 0.5% in the second and to 0.3% in the most recent cohort. In comparison with cohort A, a 7.2-fold decrease in early colectomy risk was observed in cohort B [adjusted HR 0.14; 95% CI 0.04–0.47] and a 7.4-fold decrease in cohort C [adjusted HR 0.14; 95% CI 0.04–0.46]. No difference was

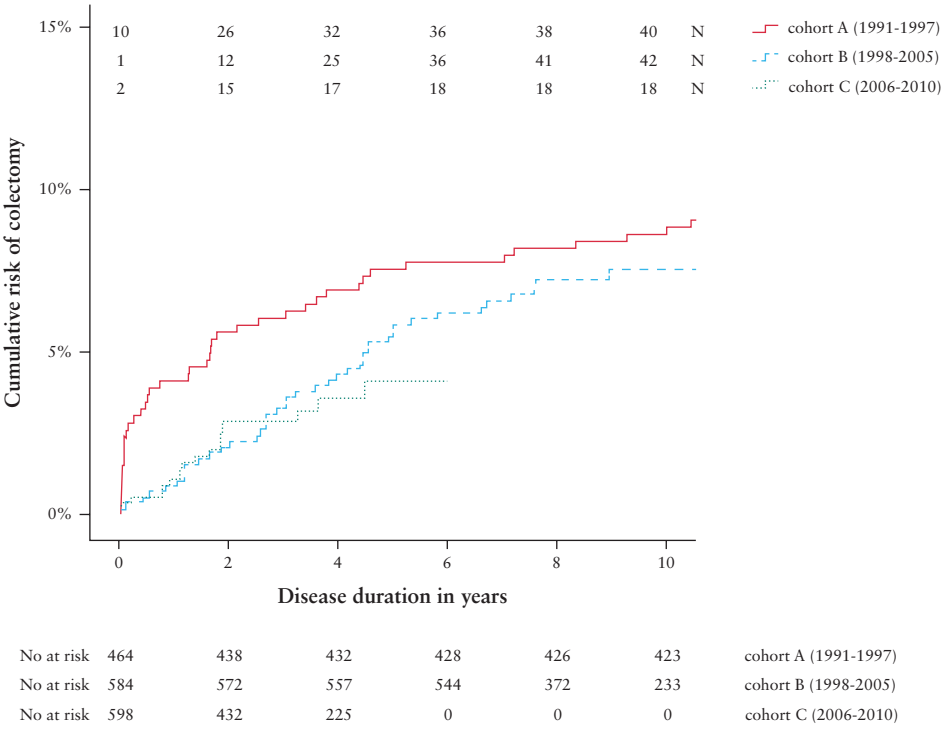

Figure 2. Cumulative risk of colectomy in UC patients from the three cohorts. UC, ulcerative colitis.

Table 2. Indications of the early and late colectomies performed.

		Cohort A 1991–1997 [$n = 476$]	Cohort B 1998–2005 [$n = 587$]	Cohort C 2006–2010 [$n = 598$]
Early colectomy	*N*	17	3	3
acute severe colitis	*N* [%]	13 [76.5]	3 [100]	3 [100]
chronic active disease	*N* [%]	1 [5.9]	-	-
unknown	*N* [%]	3 [17.6]	-	-
Late colectomy	*N*	34	40	15
acute severe colitis	*N* [%]	13 [38.2]	16 [40.0]	9 [60.0]
chronic active disease	*N* [%]	12 [35.3]	15 [37.5]	6 [40.0]
colorectal malignancy	*N* [%]	1 [2.9]	1 [2.5]	-
other	*N* [%]	1 [2.9]	3 [7.5]	-
unknown	*N* [%]	7 [20.6]	5 [12.5]	-

found between the two more recent cohorts [adjusted HR 0.98; 95% CI 0.20–4.85].

In the group of patients that did not undergo surgery within 6 months, the 5-year colectomy risk was 4.0% in cohort A, 5.2% in cohort B, and 3.6% in cohort C. No statistically significant change in late colectomy risk was observed between cohorts [$p = 0.54$]. The results were similar when the first two cohorts were combined and subsequently compared with cohort C [$p = 0.58$].

3.4. Hospitalisation

In cohort A, 288 UC-related hospitalisations took place in 155 patients, at a median of one admission per patient [range 1–12]. In cohort B, 146 patients were ever hospitalised and counted for a total of 258 hospitalisations [median of one admission per patient, range 1–6]. In the most recent cohort, 129 hospitalisations occurred in 84 patients, with a median of one admission per patient [range 1–6].

The cumulative risk of first hospitalisation after a time span of 1, 2, and 5 years was 11.9%, 16.7%, and 22.3% in cohort A, 8.6%, 11.8%, and 19.5% in cohort B, and 8.7%, 11.0%, and 18.3% in cohort C, respectively [see also Figure 3]. Compared with the first cohort, no statistical differences between hospitalisation risks were observed: adjusted HR 0.82; 95% CI 0.65–1.03 [cohort B] and adjusted HR 0.74; 95% CI 0.56–1.01 [cohort C] [Table 4]. Nor were differences observed between the second and third cohort [adjusted HR 0.96; 95% CI 0.72–1.28]. The median number of days per hospital admission decreased over time, from 17 days [IQR 12–26] in cohort A, to 15 days [IQR 10–24] in cohort B, to 13 days [IQR 8–19] in cohort C, $p < 0.01$.

The cumulative 5-year probability of rehospitalisation during disease course was 37.2% in the first, 48.6% in the second, and 44.8% in the most recent cohort. In contrast to the first cohort, rehospitalisation was more likely to occur in the second [adjusted HR 1.55; 95% CI 1.09–2.22], whereas no statistically significant effect was observed in the third cohort [adjusted HR 1.11; 95% CI 0.69–1.81].

4. Discussion

In the Dutch South-Limburg area, the risk of early colectomy has decreased over time, albeit no further risk reduction was observed in the most recent cohort diagnosed until 2010. Late colectomy rate was found to be stable over time, as was the hospitalisation rate. Duration of hospital admission gradually decreased over time.

This is the first study to assess UC disease outcome in the era of current treatment strategies, including availability of biologicals, in direct comparison with previous eras in the same source population. We studied the time trend in disease outcome since the early 90s and could reflect on the clinically relevant questions regarding the effectiveness of treatment changes in UC management at population level. The colectomy rate observed in cohort A [4.1% after 1 year, 7.5% after 5 years] was comparable to the rate observed in other population-based studies from the 90s, such as the Scandinavian IBSEN cohort [3.5% and 7.6%], the Canadian UMIBDED cohort [3.6% and 7.6%], the French EPIMAD cohort [4.0% and 8.0%], and the European EC-IBD cohort [4.7% after 2 years].[3,7,11,37]

The present study observed a decline in colectomy rate between patients diagnosed between 1991 and 1997 and patients diagnosed between 1998 and 2005. Current literature is inconsistent with respect to the question whether the colectomy rate has changed over time. A recent study in the UMIBDED cohort has shown that late colectomy rate [> 90 days after diagnosis] was 47% lower in UC patients diagnosed between 2002 and 2008, compared with patients diagnosed between 1987 and 1991. The declining colectomy rate was suggested to be the result of an increasing adoption of immunomodulators in more recent UC cohorts.[11] Conversely, in Olmsted

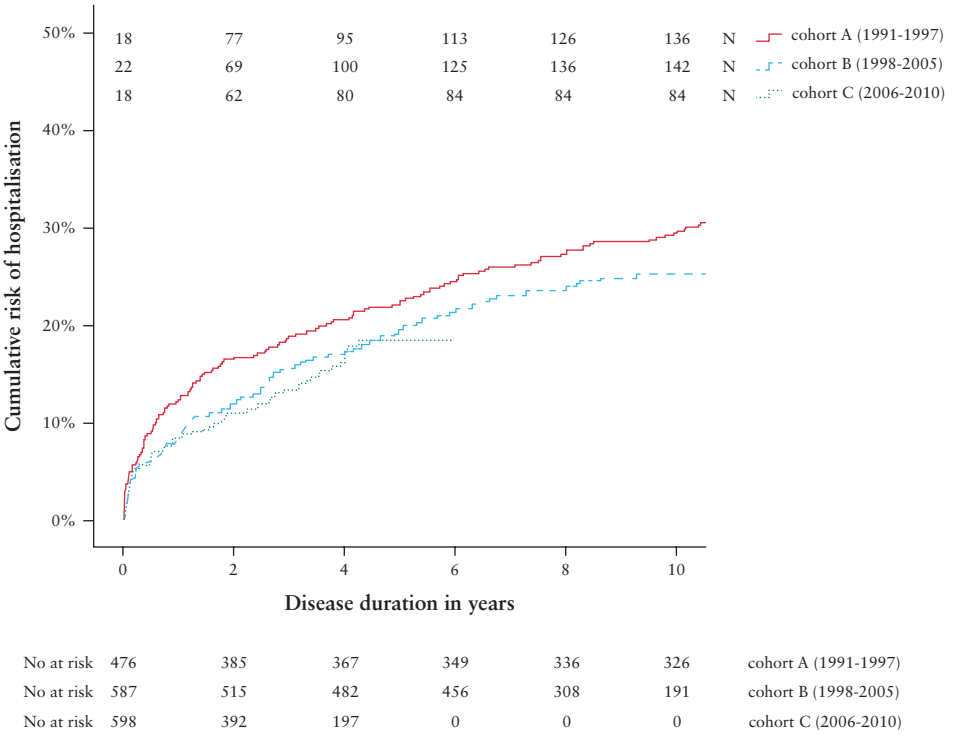

Figure 3. Cumulative risk of hospitalisation in UC patients from the three cohorts. UC, ulcerative colitis.

Table 3. Parameters associated with early and late colectomy as determined by the multivariable Cox regression model.

	Early colectomy risk [within 6 months after diagnosis]		Late colectomy risk [beyond 6 months after diagnosis]		
		Unadjusted hazard ratio[a]		Unadjusted hazard ratio	Adjusted hazard ratio[b]
	N	HR [95% CI]	*N*	HR [95% CI]	HR [95% CI]
Cohort					
cohort A [1991–1997]	17/476	Ref	34/476	Ref	Ref
cohort B [1998–2005]	3/587	0.14 [0.04–0.47]	40/587	1.26 [0.77–2.04]	1.24 [0.76–2.03]
cohort C [2006–2010]	3/598	0.14 [0.04–0.46]	15/598	0.96 [0.50–1.85]	0.97 [0.50–1.88]
Age at diagnosis					
18–40 years	10/707	Ref	50/707	Ref	Ref
41–60 years	9/581	1.09 [0.44–2.68]	22/581	0.58 [0.35–0.96]	0.61 [0.37–1.01]
> 60 years	4/373	0.76 [0.24–2.41]	17/373	0.73 [0.42–1.27]	0.73 [0.42–1.28]
Sex					
male	17/886	Ref	45/886	Ref	Ref
female	6/777	0.40 [0.16–1.01]	44/777	1.16 [0.76–1.74]	1.22 [0.80–1.85]
Disease location at diagnosis					
E1: proctitis	2/565	Ref	17/565	Ref	Ref
E2: left-sided disease	5/789	3.55 [0.41–30.36]	45/789	1.67 [0.96–2.92]	1.78 [1.01–3.13]
E3: extensive disease	16/296	31.40 [4.16–236.74]	27/296	3.36 [1.83–6.17]	3.38 [1.83–6.24]

Ref, reference category; HR, hazard ratio; CI, confidence interval.

[a]Due to the limited number of events, no adjusted model was generated for early colectomy.

[b]In the multivariable model, every parameter was corrected for the other three parameters shown.

Table 4. Parameters associated with hospitalisation and rehospitalisation as determined by the multivariable Cox regression model.

	Hospitalisation risk			Rehospitalisation risk		
		Unadjusted hazard ratio	Adjusted hazard ratio[a]		Unadjusted hazard ratio	Adjusted hazard ratio[a]
	N	HR [95% CI]	HR [95% CI]	*N*	HR [95% CI]	HR [95% CI]
Cohort						
cohort A [1991–1997]	155/476	Ref	Ref	66/145	Ref	Ref
cohort B [1998–2005]	146/587	0.83 [0.66–1.05]	0.82 [0.65–1.03]	63/123	1.42 [1.00–2.01]	1.55 [1.09–2.22]
cohort C [2006–2010]	84/598	0.75 [0.57–1.01]	0.74 [0.56–1.01]	25/84	1.06 [0.66–1.70]	1.11 [0.69–1.81]
Age at diagnosis						
18–40 years	180/707	Ref	Ref	85/165	Ref	Ref
41–60 years	101/581	0.69 [0.54–0.88]	0.73 [0.57–0.94]	34/91	0.70 [0.47–1.04]	0.64 [0.42–0.96]
> 60 years	104/373	1.23 [0.97–1.57]	1.25 [0.97–1.60]	35/96	0.74 [0.50–1.09]	0.70 [0.47–1.05]
Sex						
male	218/886	Ref	Ref	82/198	Ref	Ref
female	167/777	0.89 [0.73–1.09]	0.96 [0.78–1.18]	72/154	1.13 [0.82–1.55]	1.10 [0.80–1.52]
Disease location at diagnosis						
E1: proctitis	78/565	Ref	Ref	33/68	Ref	Ref
E2: left-sided disease	202/789	1.86 [1.43–2.43]	1.79 [1.37–2.34]	77/186	0.75 [0.50–1.12]	0.80 [0.53–1.20]
E3: extensive disease	105/296	3.13 [2.33–4.20]	3.05 [2.27–4.11]	44/96	0.97 [0.62–1.53]	1.00 [0.63–1.57]

Ref, reference category; HR, hazard ratio; CI, confidence interval.

[a]In the multivariable model, every parameter was corrected for the other three parameters shown.

County, Minnesota, a higher 5-year cumulative colectomy rate was observed in patients diagnosed between 2000 and 2004 compared with patients diagnosed between 1990 and 1999 [24.2% vs 13.1%, respectively]. The obvious increase was explained as being the result of an increase in the incidence of refractory *Clostridium difficile*-associated disease.[38] The colectomy rate in the area of Veszprem, Hungary, was reported to be stable over time.[39,40] Some time trend studies observed a decrease in the annual colectomy rate over time, but did not take the era of patients' diagnosis and disease course into account.[12,13,22] These contradicting conclusions indicate that time trends in colectomy rate differ between UC populations, illustrating the importance of studying time trends in disease outcome in the same source population. Area-specific factors, such as microbial superinfections, treatment availability, adoption of treatment strategies, and attitude towards surgery, may contribute to the differences between populations.

The decline in colectomy rate observed in the present study was mainly driven by a decrease in the risk of colectomy within 6 months after diagnosis [early colectomy]. As the colectomy rate had already decreased shortly after diagnosis, the reasons for this decline might

reside in an improved diagnostic process, ie increased awareness of the disease among patients and general practitioners, resulting in a shorter patient or physician delay. Regrettably, data on time between onset of complaints and diagnosis were not available for study. Advances in and availability and application of therapeutic options may also have contributed to the observed decrease in early colectomy risk. In line with this presumption, we documented that immunomodulatory agents were earlier and more frequently used in patients from cohort B and changes herein were already observed within the time window of early colectomy. In previous studies, it has been hypothesised that changes in the timing of, and indication for, immunomodulating therapy played an important role in observed decreasing colectomy rates.[11,12,13] A change in the role of surgery in patients with acute, severe disease was probably not causing the decline in colectomy rate, as the frequency of rescue therapy was equal in the first two cohorts. Under the current treatment strategy, the advent of biologicals seemed not to have resulted in a further decrease in early colectomy risk, as the colectomy rate in the biological era [cohort C] was not different from the last cohort of the prebiological era [cohort B]. Of note, the actual number of patients in cohort C who received biological treatment within 6 months after diagnosis was low: none of the patients received rescue therapy and only 2.7% were prescribed IFX as maintenance treatment at that stage.

Late colectomy risk was found to be similar among all three time cohorts. This observation is of interest, acknowledging the changes in the therapeutic armamentarium and treatment strategies in the past two decades. In the present cohort of UC patients, we observed a strong increase in the use of immunomodulators and biological agents. In addition, a decrease in the time to initiation of these treatment options was observed, indicative of a change in treatment strategy. Data on the long-term disease outcome of UC patients on immunomodulator therapy are lacking. Follow-up data from the ACT trials showed a lower colectomy rate in UC patients on IFX therapy compared with patients on placebo after 54 weeks [10% vs 17%, respectively].[21] Although in line with the available guidelines[33,34] and other population-based cohorts,[6,13] the number of UC patients on immunomodulator and anti-TNFα therapy is rather low, even in the most recent cohort [21.7% and 10.6%, respectively]. Whether a more common use of immunomodulators or anti-TNFα agents would result in a lower late colectomy rate is a very relevant question, but cannot be answered by our real-life, observational data. Moreover, the follow-up of patients in cohort C was considerably shorter [median 3.3 years] than that of cohort A [median 17.5 years] and cohort B [median 9.5 years], because IFX was registered for UC only in 2006. Although previous data from the EC-IBD study showed that the majority of colectomies are performed within 2 years after diagnosis,[7] future studies with a longer follow-up of patients in the biological era should further reflect the advent of anti-TNFα availability on the long-term surgery rate in UC. Ultimately, our data suggest that the changes in UC management have not resulted in a lower late colectomy rate, at least not under the currently recommended treatment strategy.

The hospitalisation rate in the 90s of the present study is comparable to the one observed in the Olmsted County. Samuel *et al.* found a cumulative probability of UC-related hospitalisation of 28.6% after 5 years,[38], in comparison with the 22.3% [cohort A] observed in the present study. However, a difference in the time trend was observed between studies, as Samuel *et al.* observed an increase to 44.2% in more recently diagnosed patients, whereas we observed a decline to 18.3% in the most recent cohort. This disparity may be explained by a difference in *Clostridium difficile*-related hospitalisation as this was suggested to have contributed to the strong rise in hospitalisation rate in the Olmsted County. In The Netherlands, the prevalence of *Clostridium difficile* is low and it is not a common trigger for IBD exacerbations.[41]

The main limitation of our study is its observational design. As a result, we cannot assess a causal relationship between the decreased risk of early colectomy and changes in early UC management, such as the early introduction of immunomodulatory agents. In general, in retrospective studies the effects of gradually adopted changes in disease management, such as the implementation of guidelines, or increased disease awareness, and also the gradual adoption of immunomodulators, cannot be assessed accurately. Furthermore, information regarding smoking status and duration of corticosteroid use was not available. Smoking is associated with a better long-term prognosis of UC, and smoking cessation results in a more aggressive disease course thereafter.[42,43] In general smoking is decreasing in The Netherlands which, if having influence, would have resulted in a more severe disease course over time. Detailed information regarding corticosteroid use would have given insight into the prevalence of steroid-dependent and steroid-refractory disease. Additionally, it is regarded as a marker for average disease course severity, which would have been an interesting outcome parameter in the comparison of the three time cohorts.

Strengths of this study reside in its strict population-based origin, high coverage, and the long period of patient inclusion. The latter offered the opportunity to assess time trends in disease outcome in decades in which marked changes in UC management have taken place. In particular, the inclusion of patients diagnosed after clinical availability of IFX delineated the effect of biological availability on disease outcome. In addition, population-based cohort studies have external validity as they are the best available instrument to study the impact of new therapies in a real-life setting of unselected patients at population level.[44,45]

In conclusion, in the Dutch population-based IBDSL cohort, a decline in early colectomy rate was observed over the past two decades, although no further reduction was observed in the most recent era. Late colectomy rate and hospitalisation rate remained unchanged over time, although duration of hospital stay reduced. These results provide an update on the prognosis of UC patients diagnosed nowadays.

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Conflict of Interest

MP has acted as consultant for MSD and Takeda and received payments for lectures from MSD, Falk Pharma, Abbvie, and Ferring. AB has received payments from Abbott, AbbVie, Ferring, Merck, MSD, Nefarma, Pfizer, Takeda, Toray, Tramedico, and Vifor concerning consultation or lectures. AM has received research funding from DSM, Grunenthal, Abbvie, and Danone.

Conference presentation

Digestive Disease Week 2013 [Orlando, FL, USA]

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