ORIGINAL RESEARCH

Long-term prognosis of ulcerative colitis and its temporal changes between 1986 and 2015 in a population-based cohort in the Songpa-Kangdong district of Seoul, Korea

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ABSTRACT

Objective No population-based study has evaluated the natural course of UC over three decades in non-Caucasians. We aimed to assess the long-term natural course of Korean patients with UC in a population-based cohort.

Design This Korean population-based, Songpa-Kangdong IBD cohort included all patients (n=1013) newly diagnosed with UC during 1986–2015. Disease outcomes and their predictors were evaluated.

Results During the median follow-up of 105 months, the overall use of systemic corticosteroids, thiopurines and antitumour necrosis factor (anti-TNF) agents was 40.8%, 13.9% and 6.5%, respectively. Over time, the cumulative risk of commencing corticosteroids decreased, whereas that of commencing thiopurines and anti-TNF agents increased. During follow-up, 28.7% of 778 patients with proctitis or left-sided colitis at diagnosis experienced proximal disease extension. A total of 28 patients (2.8%) underwent colectomy, demonstrating cumulative risks of colectomy at 1, 5, 10, 20 and 30 years after diagnosis of 1.0%, 1.9%, 2.2%, 5.1% and 6.4%, respectively. Multivariate Cox regression analysis revealed that extensive colitis at diagnosis (HR 8.249, 95% CI 2.394 to 28.430), ever use of corticosteroids (HR 6.437, 95% CI 1.440 to 28.773) and diagnosis in the anti-TNF era (HR 0.224, 95% CI 0.057 to 0.886) were independent predictors of colectomy. The standardised mortality ratio in patients with UC was 0.725 (95% CI 0.508 to 1.004).

Conclusion Korean patients with UC may have a better clinical course than Western patients, as indicated by a lower colectomy rate. The overall colectomy rate has continued to decrease over the past three decades.

Significance of this study

What is already known on this subject?

- Although UC is a progressive disease, the risk of colectomy has been decreasing over time.
- It is not yet absolutely clear whether the introduction of antitumour necrosis factor (anti-TNF) agents has contributed to further reducing the colectomy rate in patients with UC.
- There is a lack of data on the long-term prognosis of UC in a non-Caucasian population-based cohort.

What are the new findings?

- The cumulative colectomy rate over 30 years is remarkably lower in a non-Caucasian population-based cohort of UC than in their Western counterparts.
- In a non-Caucasian population with a low incidence of UC, the colectomy rate for UC has been decreasing over the past 30 years along with a more frequent and earlier use of thiopurines and anti-TNF agents.

How might it impact on clinical practice in the foreseeable future?

- By understanding the ethnic differences in the disease outcomes of UC, we can establish the optimal care pathway for patients with UC according to ethnicity.

INTRODUCTION

UC is a subtype of IBD, which is a chronic relapsing disorder of the GI tract.[1] Although the aetiology of UC has not been fully elucidated, both genetic susceptibility and environmental factors are considered key components in its pathogenesis.[2] UC has traditionally been known as a disease of Caucasians in the industrialised Western world. However, over the past few decades, the incidence of UC in newly industrialised countries, including countries in Asia as well as Central and South America, has been rapidly increasing, making UC a truly global disease.[3–5] We previously published an epidemiological study using a well-defined population-based cohort in the Songpa-Kangdong district of Seoul, Korea, which showed that the incidence of UC in Korea rapidly increased from 1986 to 2015.[6]

During the past three decades, the mean annual incidence of UC in Korea has increased from 0.29/100 000 inhabitants in 1986–1990 to 5.82/100 000 inhabitants in 2011–2015.[6]

Further, the treatment paradigm for IBD has dramatically changed with the introduction of antitumour necrosis factor (anti-TNF) therapy during the past two decades, and the surgery rates for IBD are considered to have decreased.[7] However, the overall effectiveness of anti-TNF therapy in improving the outcome of IBD, such as surgery rates, remains controversial.[7 8]

Given the progressive nature and disease burden of UC, it is crucial to understand the natural course of the disease in the long term, especially in newly developed regions. However, there has been a lack of data about the long-term prognosis of UC in non-Caucasian populations. Although we previously reported the long-term prognosis of UC in an inception cohort of patients with UC, in which we suggested that Korean patients have a milder course of UC with a lower colectomy rate, these studies are limited because of their referral centre-based design.[9 10] Moreover, recent population-based studies on UC from Asian countries evaluated the prognosis of UC with a relatively short-term duration of follow-up (1 year or 5 years).[11 12] Therefore, we sought to evaluate the long-term prognosis of UC in Korean patients over a period of 30 years by using a well-established population-based cohort in the Songpa-Kangdong district of Seoul, Korea. Additionally, we evaluated the temporal trends in UC outcomes according to changes in the treatment paradigm.

METHODS

Study area and population

The Songpa-Kangdong IBD (SK-IBD) study was performed in the Songpa-Kangdong district, a well-defined administrative region in Seoul, Korea, from 1986 (year of first IBD diagnosis) to 2015, which has been described previously.[6] During the 30-year enrolment period, the population in this region was ethnically homogeneous (predominantly Koreans) and gradually increased in number, from 936 097 inhabitants in 1986 to 1 118 960 in 2015. All inhabitants were covered under a unified public medical insurance system with easy accessibility to medical care at any time.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of our research.

Case identification and ascertainment

A prospective registry for all patients with IBD was established on 1 January 1997 in the Songpa-Kangdong district. Cases detected before 1997 were retrospectively collected and those diagnosed from 1 January 1997 were prospectively enrolled.[6] The process of case identification and ascertainment has previously been described in detail.[6] Briefly, to recruit all patients diagnosed with IBD while living in the study area, all hospitals and clinics located in the study area with facilities for diagnosing or managing patients with IBD participated in this study. In addition, to capture any unreported incident cases that were referred to hospitals located outside the study area, referral centres and colorectal-anal specialty hospitals around the study area were invited to participate in the study. Moreover, we sent a questionnaire to all general and private practitioners in the study area to ensure that no case of established IBD was missed and that any suspected IBD case was referred to the study investigators for a definitive diagnosis. We also used the diagnostic codes to identify missing patients among those diagnosed before 1997. By using the unified case report forms, we collected and updated data regularly. Data quality was confirmed and maintained through careful review by two of the authors (SKY and BDY), regular investigator meetings and site visits by a central coordinator. The data used in the present study were collected until the end of 2018.

Study design

We collected baseline demographic and clinical information, including sex, age at UC diagnosis, date of UC diagnosis, interval from onset of symptoms to diagnosis, family history of IBD, smoking status at diagnosis and disease extent at diagnosis, by using unified case report forms. In addition, we evaluated the rates of medication use, remission, relapse, proximal disease extension, colectomy and survival throughout the follow-up period to investigate the subsequent disease progression. To assess the temporal trends in treatment paradigms and in the prognosis of UC, patients were divided into three consecutive cohorts according to year of diagnosis: cohort 1, 1986–1999; cohort 2, 2000–2009; and cohort 3, 2010–2015.

The definitions used in this study have been described in previous studies. Briefly, UC diagnosis was based on the combination of conventional clinical, endoscopic, radiological and histopathological criteria.[13] The date of diagnosis was defined as the date of the first endoscopy with findings consistent with those of UC. If the diagnosis was changed from Crohn's disease (CD) or IBD unclassified to UC during follow-up, the date of the initial IBD diagnosis was considered the date of diagnosis.[14] Disease extent was classified as ulcerative proctitis (E1), left-sided UC (E2) and extensive UC (E3) according to the Montreal classification.[15] Proximal disease extension was defined as the extension of macroscopic inflammation beyond the initially involved segment (ie, from proctitis to left-sided or extensive colitis, or from left-sided colitis to extensive colitis), as determined with endoscopy.[16] Remission was defined as clinical improvement that resulted in a bowel frequency of not more than three times per day and the absence of rectal bleeding.[17] Relapse was defined as a change in the clinical status that entailed more aggressive treatment in patients in remission.[18] The use of corticosteroids at diagnosis was defined as the initiation of these drugs within 1 month of UC diagnosis.

Treatment policy

The strategies for treating UC in Korea are similar to those in Western countries and have been previously described in detail.[10 19] Briefly, topical and/or oral 5-aminosalicylates are first-line therapies for inducing and maintaining remission in mild-to-moderate UC. Oral corticosteroids are used in patients with moderate-to-severe UC or in those unresponsive to 5-aminosalicylates. Corticosteroids are tapered off over 2–3 months. Thiopurines (azathioprine/6-mercaptopurine) and, in case of their failure, anti-TNF agents are used in patients with steroid-dependent or steroid-refractory UC. For hospitalised patients with acute severe UC, intravenous corticosteroids are considered the first-line therapy. A rescue medical therapy with anti-TNF agents or intravenous ciclosporin or colectomy is considered in patients unresponsive to intensive corticosteroid treatment. For the treatment of UC in Korea, thiopurines began to be used mainly in the 2000s and anti-TNF agents have been covered by insurance since 2010. Owing to the strict criteria for government reimbursement of anti-TNF therapy, anti-TNF agents can only be used for patients with moderate or severe disease activity who are unresponsive to conventional treatment

with corticosteroids and/or thiopurines. Ciclosporin is only rarely used and therefore excluded from the present analysis. Patients are followed up at regular intervals, usually every 1–3 months, according to their conditions.

Statistics

Continuous variables are presented as medians with IQRs, whereas categorical variables are presented as numbers with percentages. The t-test or Mann-Whitney U test was used to compare continuous variables, and the χ^2 test or Fisher's exact test was used to compare categorical variables, as appropriate. Cumulative probabilities of medication use, remission, relapse, proximal disease extension, colectomy and survival were calculated using the Kaplan-Meier method, and the values were compared between groups by using the log-rank test. Multivariate Cox regression analysis with the stepwise selection method was performed to identify significant predictors of the cumulative probabilities of proximal disease extension and colectomy, and to calculate their HRs and 95% CIs. To compare the mortality of patients with UC with that of the general population, the standardised mortality ratio (SMR) (ie, the ratio of observed to expected number of deaths) was calculated.[20] The Poisson distribution was used to calculate the 95% CIs of SMRs. The mortality data of the entire Korean population were obtained from the Korean Statistical Information Service.[21] A p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS V.21.0 for Windows or SAS V.9.4.

RESULTS

Baseline characteristics

A total of 1013 patients were diagnosed with UC from January 1986 to December 2015: 152 in 1986–1999 (cohort 1), 445 in 2000–2009 (cohort 2) and 416 in 2010–2015 (cohort 3). Table 1 summarises the demographic and clinical characteristics of the patients. There were no significant differences in the proportion of men, age at diagnosis and interval from symptom onset to diagnosis among the three temporal cohorts. However, the proportion of current smokers at diagnosis ($p=0.003$) and that of patients with proctitis at diagnosis ($p<0.001$) significantly increased from cohort 1 to cohort 3.

Medical treatment

The median follow-up duration was 105.1 months (IQR, 60.3–169.9 months). All patients had ever use of oral or topical 5-aminosalicylates. Systemic corticosteroids, thiopurines and anti-TNF agents were administered to 40.8%, 13.9% and 6.5%, respectively, of patients at diagnosis and/or during follow-up. The median interval from UC diagnosis to medication initiation was 4.3 months (IQR, 0.1–29.2 months) for corticosteroids, 32.9 months (IQR, 14.4–78.6 months) for thiopurines and 45.5 months (IQR, 19.3–117.1 months) for anti-TNF agents. The cumulative risks of commencing medications at 1, 5, 10 and 20 years after diagnosis were 25.4%, 36.8%, 42.6% and 52.2%, respectively, for corticosteroids; 3.3%, 9.7%, 13.8% and 21.5%, respectively, for thiopurines; and 1.2%, 4.1%, 6.3% and 11.1%, respectively, for anti-TNF agents. Figure 1 presents the temporal changes in the cumulative risk of commencing medications over the past three decades. The cumulative risk of commencing corticosteroids significantly decreased ($p<0.001$), whereas that of commencing thiopurines and anti-TNF agents significantly increased ($p=0.004$ and $p<0.001$, respectively). Additionally, the median interval from UC diagnosis to commencing thiopurines and anti-TNF agents decreased from 149.3 and 198.2 months, respectively, in cohort 1 to 15.4 and 29.0 months, respectively, in cohort 3 (both $p<0.001$).

Remission and relapse

Among the 1013 patients, 944 (93.2%) achieved clinical remission. Clinical remission was not documented in 29 (2.9%) patients.

Table 1 Demographic and clinical characteristics of 1013 patients with UC in the Songpa-Kangdong district of Seoul, Korea, in 1986–2015

	Year of diagnosis			
Clinical characteristics	**Cohort 1 (1986–1999)**	**Cohort 2 (2000–2009)**	**Cohort 3 (2010–2015)**	**Total**
Number of patients, n (%)	152 (15.0)	445 (43.9)	416 (41.1)	1013 (100)
Male sex, n (%)	72 (47.4)	248 (55.7)	223 (53.6)	543 (53.6)
Median age at diagnosis (IQR), years	36 (25–43)	36 (27–47)	36 (27–52)	36 (27–48)
Age at diagnosis, n (%), years				
≤16	11 (7.2)	13 (2.9)	13 (3.1)	37 (3.7)
17–40	88 (57.9)	259 (58.2)	226 (54.3)	573 (56.6)
>40	53 (34.9)	173 (38.9)	177 (42.5)	403 (39.8)
Median interval from onset to diagnosis (IQR), months	5.9 (2.0–13.2)	2.6 (1.0–8.5)	2.4 (0.9–7.8)	2.8 (1.0–9.3)
Smoking status at diagnosis, n (%)				
Never smoker	111 (73.0)	225 (50.6)	212 (51.0)	548 (54.1)
Former smoker	14 (9.2)	69 (15.5)	78 (18.8)	161 (15.9)
Current smoker	13 (8.6)	75 (16.9)	65 (15.6)	153 (15.1)
Disease extent at diagnosis, n (%)				
Proctitis	57 (37.5)	247 (55.5)	246 (59.1)	550 (54.3)
Left-sided colitis	53 (34.9)	101 (22.7)	74 (16.6)	228 (22.5)
Extensive colitis	42 (27.6)	97 (21.8)	96 (23.1)	235 (23.2)
Median duration of follow-up (IQR), months	261.2 (229.5–289.3)	140.9 (110.1–175.1)	64.7 (45.4–85.8)	105.1 (60.3–169.9)
Ever use of medications, n (%)				
Systemic corticosteroids	98 (64.5)	188 (42.2)	127 (30.5)	413 (40.8)
Thiopurines	25 (16.4)	61 (13.7)	55 (13.2)	141 (13.9)
Anti-TNF agents	7 (4.6)	20 (4.5)	39 (9.4)	66 (6.5)

TNF, tumour necrosis factor.

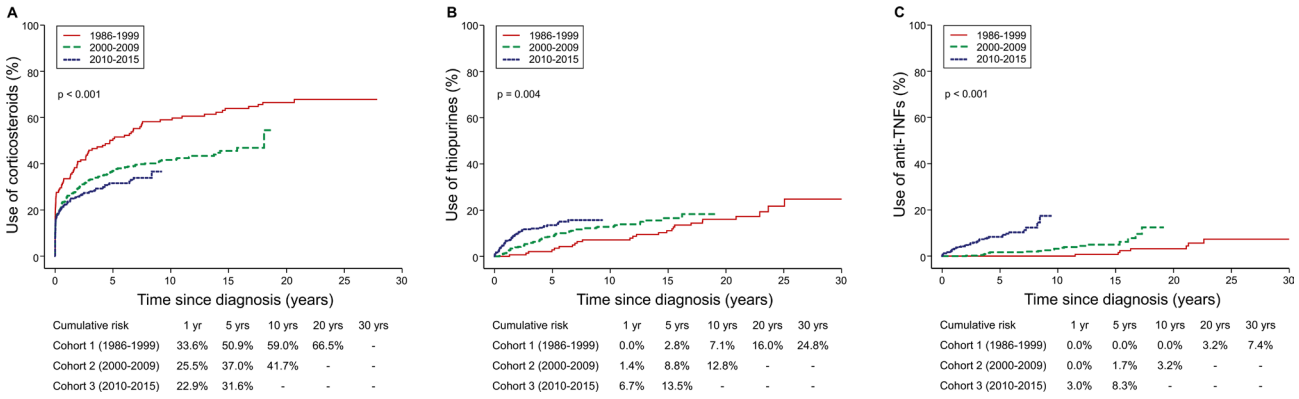

Figure 1 Temporal trends in the cumulative risk of medication use in patients with UC: (A) corticosteroids, (B) thiopurines and (C) antitumour necrosis factor (anti-TNF) agents.

Among the remaining 40 patients who did not achieve remission during follow-up, 8 underwent colectomy after a median of 1.5 months (IQR, 1.2–3.3 months) of receiving medical therapy and 32 had persistent symptoms despite marked improvement over the 39.9 months of follow-up (IQR, 16.5–54.3 months). The cumulative remission rates at 1, 5, 10 and 20 years after diagnosis were 79.0%, 92.7%, 95.1% and 95.3%, respectively. Among the 944 patients who achieved clinical remission, 689 (73.0%) experienced at least one relapse during follow-up. The median interval from remission to relapse was 14.8 months (IQR, 5.9–35.7 months). The cumulative relapse rates at 1, 5, 10 and 20 years were 33.9%, 69.7%, 82.8% and 90.8%, respectively.

Proximal disease extension

The disease extent at diagnosis was classified as proctitis in 550 patients (54.3%), left-sided colitis in 228 patients (22.5%) and extensive colitis in 235 patients (23.2%). Among the 778 patients with proctitis or left-sided colitis at diagnosis, proximal disease extension was noted in 223 (28.7%), with a median time to extension of 33.2 months (IQR, 19.3–72.5 months). The cumulative risks of proximal disease extension after 5, 10, 20 and 30 years were 20.5%, 30.2%, 46.7% and 54.0%, respectively, for all patients with proctitis or left-sided colitis at diagnosis (figure 2A). The cumulative risk of proximal disease extension was significantly higher in patients with proctitis at diagnosis than in those with left-sided colitis at diagnosis (p<0.001; figure 2B). The Kaplan-Meier estimates of the proportion of patients according to the maximum disease extent at 10, 20 and 25 years were 35.6%, 23.4% and 21.7%, respectively, for proctitis; 29.7%, 34.3% and 30.7%, respectively, for left-sided colitis; and 34.7%, 42.3% and 47.6%, respectively, for extensive colitis. The cumulative risks of proximal disease extension were comparable across the three temporal cohorts (p=0.790; figure 2C). Multivariate Cox regression analysis revealed that corticosteroid use at diagnosis (HR 2.020, 95%CI 1.401 to 2.911) and disease extent at diagnosis (HR_{E2} 0.483, 95%CI 0.347 to 0.671) were independent predictors of proximal disease extension (table 2).

Hospitalisation

A total of 178 (17.6%) patients experienced at least one hospitalisation that required systemic corticosteroids, immunomodulators, anti-TNF agents or colectomy at diagnosis or during follow-up. The median number of hospitalisations per patient was 1 (IQR, 1–2), and the median time to the first hospitalisation was 3.4 months (IQR, 0.0–35.9 months). The cumulative risks of hospitalisation at 1, 5 and 10 years after diagnosis were 10.6%, 15.1% and 18.4%, respectively (figure 3A). The cumulative risk of hospitalisation was significantly higher in cohort 1 than in cohorts 2 and 3 (p<0.001; figure 3B). Multivariate Cox analysis revealed that disease extent at diagnosis (HR_{E2} 1.612, 95%CI 1.020 to 2.549; HR_{E3} 4.369, 95%CI 2.949 to 6.474) and corticosteroid use at diagnosis (HR 5.944, 95%CI 4.320 to 8.179) were independent predictors of hospitalisation (table 3).

Colectomy

In total, 28 patients (2.8%) underwent colectomy during the follow-up. The indications for colectomy included refractory symptoms on maximum medical therapy in 16 patients (57.1%),

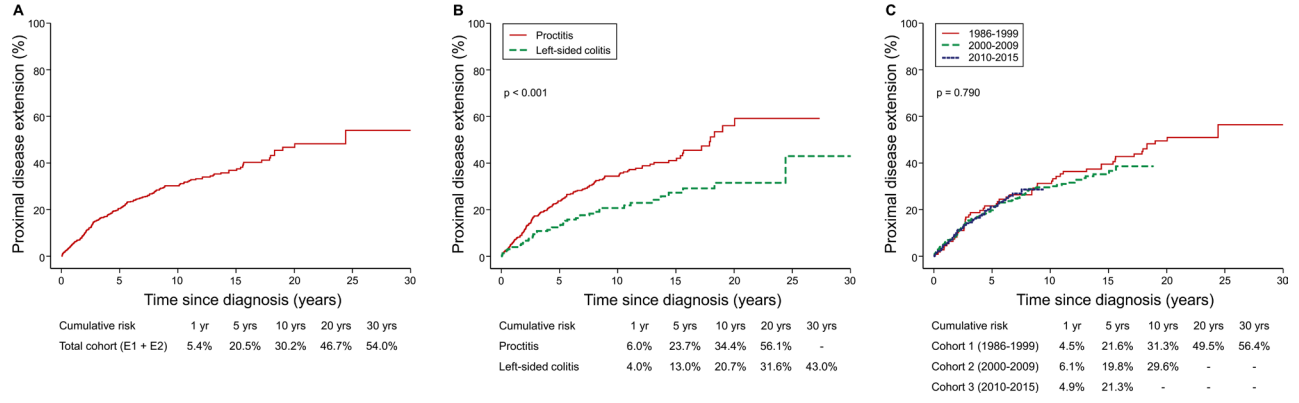

Figure 2 Cumulative risk of proximal disease extension in patients with UC: (A) in the total cohort, (B) according to the disease extent at diagnosis and (C) in the three temporal cohorts.

Table 2 Risk factors for proximal disease extension in patients with UC

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Female	Reference		Reference	
Male	1.242 (0.953 to 1.619)	0.109	1.208 (0.887 to 1.644)	0.231
Age at diagnosis, years				
≤16	Reference		Not included	
17–40	0.768 (0.374 to 1.575)	0.471		
>40	0.755 (0.366 to 1.559)	0.448		
Smoking status at diagnosis				
Never smoker	Reference		Reference	
Former smoker	1.498 (1.084 to 2.070)	0.014	1.279 (0.889 to 1.839)	0.185
Current smoker	0.940 (0.634 to 1.394)	0.759	0.829 (0.542 to 1.270)	0.390
Family history of IBD				
No	Reference		Not included	
Yes	0.745 (0.395 to 1.406)	0.363		
Disease extent at diagnosis				
Proctitis	Reference		Reference	
Left-sided colitis	0.533 (0.387 to 0.735)	<0.001	0.483 (0.347 to 0.671)	<0.001
Use of corticosteroids at diagnosis				
No	Reference		Reference	
Yes	1.702 (1.191 to 2.432)	0.004	2.020 (1.401 to 2.911)	<0.001
Cohorts				
1986–1999	Reference		Not included	
2000–2009	0.885 (0.622 to 1.260)	0.499		
2010–2015	0.930 (0.623 to 1.389)	0.724		

corticosteroid dependency/intolerance in 4 patients (14.3%), colorectal dysplasia/cancer in 6 patients (21.4%), perforation in 1 patient (3.6%) and obstruction in 1 patient (3.6%). The indication of colectomy appears to have changed over time. Of the 20 patients who underwent colectomy during the first 10 years after diagnosis, 75% had colectomy for medical refractoriness, 20% for corticosteroid dependency/intolerance and 5% for perforation. In contrast, of the eight patients who underwent colectomy after 10 years following diagnosis, 75% had colectomy for dysplasia/cancer, 12.5% for medical refractoriness and 12.5% for obstruction. Among the 66 patients who were receiving anti-TNF therapy, 5 (7.6%) underwent colectomy after receiving anti-TNF therapy for a median of 3.9 months (0.2, 0.9, 3.9, 9.7 and 10.5 months). The cumulative risks of colectomy at 1, 5, 10, 20 and 30 years after diagnosis were 1.0%, 1.9%, 2.2%, 5.1% and 6.4%, respectively (figure 4A). When separately analysed according to disease extent at diagnosis, the risks were 0.0%, 0.4%, 0.4%, 1.3% and 1.3%, respectively, for patients with proctitis; 0.9%, 1.4%, 1.4%, 3.8% and 7.4%, respectively, for those with left-sided colitis; and 3.4%, 5.8%, 7.2%, 15.1% and 15.1%, respectively, for those with extensive colitis (p<0.001; figure 4B). The cumulative risk of colectomy significantly decreased over the past 30 years (p=0.01; figure 4C). A comparison of the colectomy rate between patients diagnosed in the pre-anti-TNF era (cohorts 1 and 2) and those diagnosed in the anti-TNF era (cohort 3) revealed that the cumulative risk of colectomy was lower in the anti-TNF era (p=0.001). Multivariate Cox regression analysis revealed that disease extent at

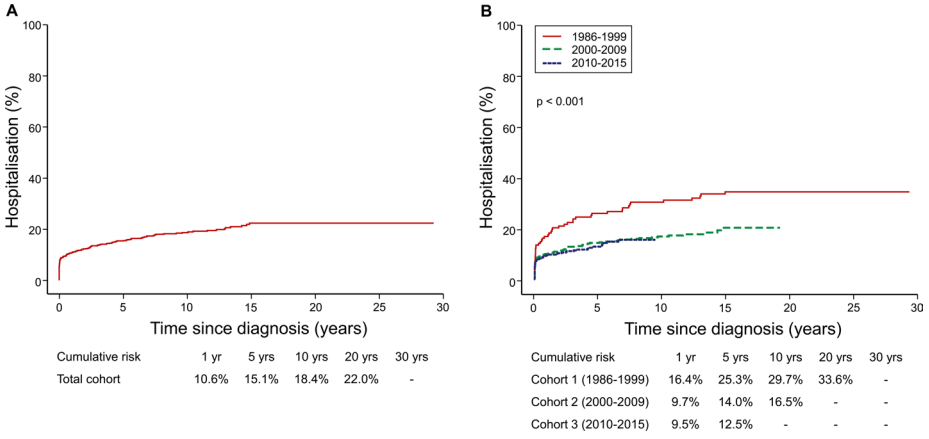

Figure 3 Cumulative risk of hospitalisation in patients with UC: (A) in the total cohort and (B) in the three temporal cohorts.

Table 3 Risk factors for hospitalisation in patients with UC

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Female	Reference		Not included	
Male	0.865 (0.645 to 1.161)	0.335		
Age at diagnosis, years				
≤16	Reference		Reference	
17–40	0.626 (0.337 to 1.163)	0.138	1.228 (0.658 to 2.292)	0.519
>40	0.384 (0.200 to 0.736)	0.004	1.109 (0.572 to 2.152)	0.759
Smoking status at diagnosis				
Never smoker	Reference		Not included	
Former smoker	0.929 (0.617 to 1.399)	0.725		
Current smoker	0.740 (0.471 to 1.163)	0.192		
Family history of IBD				
No	Reference		Not included	
Yes	0.707 (0.332 to 1.507)	0.369		
Disease extent at diagnosis				
Proctitis	Reference		Reference	
Left-sided colitis	2.176 (1.387 to 3.413)	0.001	1.612 (1.020 to 2.549)	0.041
Extensive colitis	7.854 (5.444 to 11.331)	<0.001	4.369 (2.949 to 6.474)	<0.001
Use of corticosteroids at diagnosis				
No	Reference		Reference	
Yes	9.133 (6.773 to 12.317)	<0.001	5.944 (4.320 to 8.179)	<0.001
Cohorts				
1986–1999	Reference		Reference	
2000–2009	0.529 (0.368 to 0.759)	0.001	0.726 (0.504 to 1.045)	0.085
2010–2015	0.496 (0.334 to 0.737)	0.001	0.696 (0.466 to 1.040)	0.077

diagnosis (HR_{E3} 8.249, 95% CI 2.394 to 28.430), ever use of corticosteroids (HR 6.437, 95% CI 1.440 to 28.773) and year of diagnosis ($HR_{2010–2015}$ 0.224, 95% CI 0.057 to 0.886) were independent predictors of colectomy (table 4).

Mortality

Overall, 36 patients (3.6%) died within a median follow-up of 97.5 months (IQR, 49.3–127.0 months) after diagnosis. The cumulative survival rates were 99.7% at 1 year, 98.7% at 5 years, 96.6% at 10 years, 92.2% at 20 years and 91.2% at 30 years. The SMR in patients with UC was 0.725 (95% CI 0.508 to 1.004).

DISCUSSION

In this study, we evaluated the long-term clinical course of UC in Korea by using a well-defined population-based cohort (SK-IBD). To our knowledge, this is the first study to evaluate the long-term prognosis of UC over 30 years in a non-Caucasian population.

The most important finding of the present population-based study is that the cumulative risk of colectomy in Korean patients with UC was much lower than that in Western patients with UC. According to a recent meta-analysis of Western population-based studies, the cumulative risk of colectomy at 1, 5 and 10

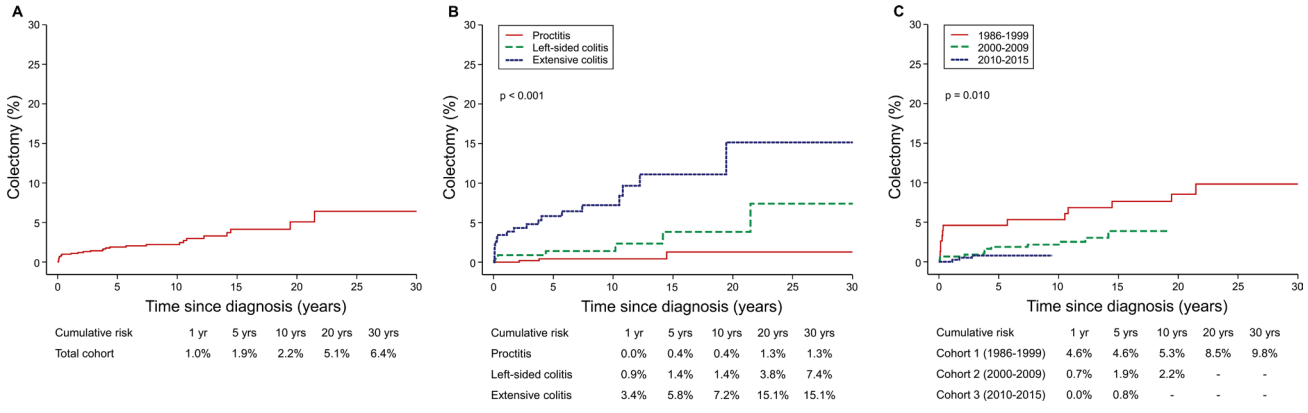

Figure 4 Cumulative risk of colectomy in patients with UC: (A) in the total cohort, (B) according to the disease extent at diagnosis and (C) in the three temporal cohorts.

Table 4 Risk factors for colectomy in patients with UC

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex				
Female	Reference		Not included	
Male	0.922 (0.439 to 1.936)	0.830		
Age at diagnosis, years				
≤16	Reference		Not included	
17–40	0.351 (0.100 to 1.231)	0.102		
>40	0.402 (0.111 to 1.454)	0.165		
Smoking status at diagnosis				
Never smoker	Reference		Not included	
Former smoker	1.096 (0.412 to 2.915)	0.855		
Current smoker	0.444 (0.104 to 1.898)	0.274		
Family history of IBD				
No	Reference		Not included	
Yes	0.550 (0.074 to 4.064)	0.558		
Disease extent at diagnosis				
Proctitis	Reference		Reference	
Left-sided colitis	4.218 (1.053 to 16.900)	0.042	2.827 (0.701 to 11.406)	0.144
Extensive colitis	15.320 (4.532 to 51.780)	<0.001	8.249 (2.394 to 28.430)	0.001
Cohorts				
1986–1999	Reference			
2000–2009	0.438 (0.1919 to 1.004)	0.051	0.590 (0.254 to 1.370)	0.220
2010–2015	0.169 (0.045 to 0.630)	0.008	0.224 (0.057 to 0.886)	0.033
Ever use of medications				
Systemic corticosteroids	15.620 (3.695 to 66.000)	<0.001	6.437 (1.440 to 28.773)	0.015
Thiopurines	2.980 (1.373 to 6.469)	0.006	1.287 (0.517 to 3.208)	0.588
Anti-TNF agents	3.144 (1.194 to 8.275)	0.020	1.493 (0.462 to 4.829)	0.503

TNF, tumour necrosis factor.

years after UC diagnosis was 4.9%, 11.6% and 15.6%, respectively.[7] Although the cumulative risk of surgery has significantly decreased in recent years, it was still 2.7% at 1 year and 7.6% at 5 years even among patients diagnosed after 2000.[7] In contrast, the present study found that the cumulative risk of colectomy at 1, 5 and 10 years after diagnosis was only 1%, 1.9% and 2.2%, respectively. When the cumulative risk of colectomy among patients diagnosed in 2000 or later was analysed, the risk was even lower: 0.4% at 1 year, 1.4% at 5 years and 1.6% at 10 years (data not shown). Lower colectomy rates in Asian patients with UC have been reported in two population-based studies: 1.1% at 1 year in South-East Asian patients diagnosed in 2011–2013 and 1.8% at 1 year and 2.1% at 5 years in Hong Kong patients diagnosed in 1981–2014.[11 12] The colectomy rate in the present study is even lower than those reported in these Asian studies. It is unclear from these studies whether the low colectomy rate reflects a good prognosis of UC in Asian patients or a mere delay of colectomy despite the unfavourable clinical course of UC, because these Asian studies only reported short-term colectomy rates (1 year or 5 years).[11 12] The 30-year cumulative risk of colectomy in the present study was only 6.4%, which is lower than the 5-year cumulative risk of colectomy reported in Western studies.[7] Therefore, we believe that our study is the first to demonstrate that Asian patients have a better clinical course of UC than Western patients, not only in the short term but also in the long term. Regarding the trend of colectomy rate after diagnosis, previous Western studies have indicated that the risk of colectomy in UC is highest during the first 1 or 2 years after diagnosis and then decreases over time.[22 23] Our result on colectomy is comparable with this trend. Interestingly, the colectomy rate was especially low between years 5 and 10 and slightly increased after 10 years following diagnosis in the present study. This is likely due to the occurrence of dysplasia/cancer after 10 years of diagnosis.

However, the low rate of colectomy in the present study should be cautiously interpreted with the following considerations. First, our study included a high proportion of patients with proctitis at diagnosis (54.3%). This may, at least in part, explain the low colectomy rate. However, when considering only patients with extensive colitis, the cumulative risk of colectomy remained relatively low: 7.2% at 10 years, 15.1% at 20 years and 15.1% at 30 years. These values seem lower than the colectomy rates of Western patients with all disease extents combined (25% at 20 years in Olmsted County[24] and 20% at 20 years and 25% at 30 years in Uppsala[22]). Second, the cultural preferences of Korean patients may partly contribute to the lower rate of colectomy. However, avoidance or inadequate delay of colectomy in patients requiring colectomy, particularly in those with acute severe UC, may adversely affect their survival. In our study, the survival rate of patients with UC was at least as good as that of the general population (SMR: 0.725). This value falls within the lower range of SMRs (0.7–1.25) reported in previous Western population-based studies.[25–29] Thus, our study seems to show a low possibility of delayed surgery in patients requiring colectomy for medically refractory diseases. Taken together, Korean patients may have a milder course of UC than Western patients.

The cause of the better clinical course in Korean patients than in Western patients is uncertain. Genetic and environmental

factors may play roles. Although the genetic associations for UC overlap more extensively between Asian patients and patients of European ancestry than those for CD, the difference in the clinical course between these populations is more prominent in UC than in CD.[30] However, this does not necessarily indicate that environmental factors are more important than genetic factors in determining the prognosis of UC versus that of CD. It is known that most susceptibility genes or loci in IBD are not associated with prognosis, and genetic factors with prognostic significance have largely been unrevealed.[31–33] In studies on migrant Asians with UC, Asians who had migrated to Canada or England had lower risks of colectomy than native residents.[34–36] Although this result suggests that the underlying genetics is important, it also indicates that early-life environmental influences before migration exert a durable effect on disease outcomes.[37] In this regard, transethnic studies on genetic and environmental prognostic factors may be warranted. Moreover, the rate of proximal disease extension, another marker of disease progression, in this study seems similar to or slightly higher than that in previous Western reports,[22] along with a similar pattern of medication use.[22 23] However, it is difficult to compare the rate of proximal disease extension in our study with that in previous Western studies as there may be differences in the evaluation tools and intervals for detecting proximal disease extension.

Another important finding of the present study is that the colectomy rate in Korean patients with UC has been decreasing along with a significant increase in the use of thiopurines and anti-TNF agents over the past three decades. Although the proportion of proctitis at diagnosis increased during the study period, a decrease in colectomy in the recent cohort cannot be explained by this factor alone because the colectomy rate decreased even in a subset of patients with extensive colitis at diagnosis. In addition, multivariate Cox regression analysis revealed that the anti-TNF era was an independent negative predictor of colectomy. However, we could not demonstrate a causal relationship between the introduction of anti-TNF agents and the decrease in the colectomy rate. Changes in unmeasured confounders, such as an increased awareness of the disease during the study period, may have caused the decrease in the colectomy rate.

The present study has several strengths. First, the population-based design in a setting with easy accessibility to a public healthcare system in a well-defined administrative region enabled us to include unselected patients representing the entire disease spectrum. The pattern of treatment for UC reflects real-life clinical settings during the study period in Korea. Second, in contrast to studies using health administrative data, in which misclassification of patients and lack of detailed information (eg, disease extent and smoking status) are common problems,[38] our study used strict uniform criteria to confirm the diagnosis, and regularly updated the diagnosis and clinical information during follow-up. Lastly, the enrolment of patients over a period of 30 years facilitated the evaluation of temporal trends in disease outcomes according to the changes in UC management, particularly the introduction of anti-TNF agents.

However, there are some limitations to our study. First, because there are genotypic and phenotypic differences among patients with UC in different Asian countries, it is questionable whether the disease outcomes of our study can be generalised to other Asian populations.[5] For example, proctitis is more common in East Asians, whereas pancolitis is more common in Middle Eastern and South Asians.[37] Even among East Asians, the proportion of proctitis is higher in Koreans than in Chinese.[6 12] With respect to the genetic predictors of UC prognosis, the intergenic variant rs9268877 between HLA-DRA and HLA-DRB has been reported to be associated with a poor prognosis of UC in Koreans.[30] However, this association is yet to be reported in other Asian populations. Therefore, more studies are needed on UC outcomes in other Asian populations. Second, because data on the disease activity at UC diagnosis were not collected, we could not evaluate the impact of disease activity at UC diagnosis on the risk of disease progression. Instead, we used corticosteroid use at diagnosis as a surrogate marker of disease activity at diagnosis. Third, although we evaluated the first episode of remission and relapse, we could not evaluate the number of all episodes of disease flares, especially mild or transient ones. Instead, we evaluated the rate of hospitalisation for UC flares, which was lower than those reported in Western studies.[22] Fourth, we did not evaluate the rate of disease regression in terms of disease extent, which may be one of the possible explanations for the benign disease course in Korean patients with UC. Lastly, we did not obtain detailed information regarding extraintestinal manifestations (EIMs) in these patients. The frequency of EIMs in IBD was lower in East Asia than in Western countries.[39] However, a reliable assessment of the frequency of EIMs is difficult because many of them are non-specific or transient. Therefore, we evaluated only the frequency of primary sclerosing cholangitis, one of the most objectively measurable EIMs, which was observed only in five patients (0.5%) in the study population (data not shown).

In conclusion, the present population-based cohort study demonstrates that Korean patients with UC may have a better clinical course than their Western counterparts, as indicated by a lower colectomy rate even in the long term. Moreover, we showed that thiopurines and anti-TNF agents have been increasingly more frequently and earlier used, and that the colectomy rate seems to have decreased, over the past 30 years.

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