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Original Article

Clinical Characteristics and Long-term Prognosis of Elderly-Onset Ulcerative Colitis in a Population-Based Cohort in the Songpa-Kangdong District of Seoul, Korea

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Background/Aims: We aimed to evaluate the clinical characteristics and long-term prognosis of elderly-onset ulcerative colitis (EOUC) in Korean patients over a 30-year period using a well-established population-based cohort in the Songpa-Kangdong district of Seoul, Korea.

Methods: Clinical characteristics and prognosis were compared between two groups: EOUC, defined as UC diagnosed in individuals aged ≥60 years and non-EOUC (N-EOUC), defined as UC diagnosed in individuals aged 18 to 59 years.

Results: We identified 99 patients with EOUC (10.3%) and 866 patients with N-EOUC (89.7%) between 1986 and 2015. During the median follow-up of 104.5 months, the overall exposure to medications was comparable between patients with EOUC and N-EOUC (p=0.091 for corticosteroids, p=0.794 for thiopurines, and p=0.095 for anti-tumor necrosis factor agents). The cumulative risks of disease outcomes were also comparable between patients with EOUC and N-EOUC (22.4% vs 30.4% for proximal disease extension [p=0.351], 11.9% vs 18.1% for hospitalization [p=0.240], and 2.3% vs 1.8% for colectomy [p=0.977]) at 10 years after diagnosis. Multivariate Cox regression analysis revealed that corticosteroid use at diagnosis was an independent predictor of proximal disease extension (hazard ratio [HR], 6.216; 95% confidence interval [CI], 1.314 to 28.826) and hospitalization (HR, 11.241; 95% CI, 3.027 to 41.742) in patients with EOUC.

Conclusions: In this population-based study from Korea, the pattern of medication use seemed comparable between the EOUC and N-EOUC groups. Moreover, patients with EOUC and those with N-EOUC have a similar disease course in terms of proximal disease extension, hospitalization, and colectomy. **(Gut Liver 2021;15:742-751)**

Key Words: Colitis, ulcerative; Aged; Prognosis; Korea

INTRODUCTION

Ulcerative colitis (UC) is a subtype of inflammatory bowel disease (IBD), which is a chronic inflammatory condition of the intestine.[1] The incidence and prevalence of IBD are continuously increasing in the Western world and are also rapidly increasing in newly industrialized countries, making IBD a global disease.[2] As the population con-

tinues to age, the incidence and prevalence of elderly-onset (EO)-IBD, defined as the diagnosis of IBD in patients aged ≥60 years, are expected to increase continuously.[3] We previously reported an epidemiological study using a well-established population-based cohort in the Songpa-Kangdong district of Seoul, Korea, which revealed that the incidence of UC has rapidly increased between 1986 and 2015. In this study, we observed a bimodal distribution in the age at diagnosis of IBD, specifically UC, at the age of 60 to 69 years.[4] This finding seems comparable to those of several Western reports, which showed a second peak in incidence at approximately 60 years of age for IBD, probably due to the aging cohorts in these regions.[5-7]

EO-IBD usually tends to be treated conservatively with consideration of frequent comorbidities.[8,9] Moreover, chronic corticosteroid use or biologic therapies may result in higher risk of serious opportunistic infections and malignancies in this subset of patients than in younger patients.[10,11] However, whether or not the natural history and clinical outcomes of elderly-onset ulcerative colitis (EOUC) are different from those of non-EOUC (N-EOUC) remains controversial. Previous studies have suggested that patients with EOUC may have an aggressive disease course, such as higher probabilities of colectomy, compared to those with N-EOUC.[12-14] Also, recent multicenter studies from Hong Kong reported the poor outcomes of EO-IBD.[15,16] However, these studies used a referral center-based design, resulting in an inherent risk of referral bias. Additionally, a recent systematic review of a Western population-based cohort showed that EOUC patients have a comparable risk of colectomy as those with N-EOUC.[17] To date, there has been a paucity of data regarding the long-term characteristics of EOUC in a population-based level from Asian region. We, therefore, aimed to investigate the long-term outcome of EOUC in Korean patients over a 30-year period using a well-defined population-based cohort in Korea.

MATERIALS AND METHODS

1. Study patients

The Songpa-Kangdong IBD study was conducted in the Songpa-Kangdong district, a well-established administrative region in Seoul, Korea, between 1986 (the year of the first IBD diagnosis) and 2015.[4] This study protocol was approved by the institutional review boards of all involved hospitals and the Songpa-Kangdong IBD cohort is registered in ClinicalTrial.gov (NCT01731665). In this study, the informed consent was waived by the institutional review boards.

2. Study design

Based on data from previous studies,[15,16,18,19] patients with EOUC were defined as those aged ≥60 years at UC diagnosis. The clinical features and disease outcome of patients with EOUC were compared with those with N-EOUC, defined as those aged between 18 and 59 years at UC diagnosis. We gathered the information regarding patients' baseline characteristics, such as sex, age at the time of UC diagnosis, date of UC diagnosis, interval from symptom onset to diagnosis, smoking status at the time of diagnosis, family history of IBD, and disease extent of UC at diagnosis. Additionally, we investigated the rates of medication use for UC, clinical remission, disease relapse, proximal disease extension on endoscopy, and colectomy during the follow-up period to evaluate subsequent disease progression. The diagnosis of UC was based on a combination of conventional clinical, endoscopic, radiologic, and histopathologic criteria.[20] The definitions used in this study, including those for disease extent, proximal disease extension, remission, and relapse, have been described in our previous study.[21] Proximal disease extension was defined as the proximal extension of endoscopic inflammation beyond the initially involved segments (i.e., from proctitis [E1] to left-sided [E2] or extensive colitis [E3], from left-sided colitis [E2] to extensive colitis [E3]).[21] The use of corticosteroids at UC diagnosis was defined as the commencement of these drugs within a month of UC diagnosis.[21] Hospitalization was defined as admission for managing flare-ups of UC, either medically or surgically. We excluded admissions that were only for disease evaluation or drug administration, as well as those that were shorter than 3 days or unrelated to UC.[22,23]

3. Treatment strategy

In Korea, the treatment strategies for UC patients are not different from those in Western countries and have been previously explained in detail.[21] Basically, a step-up approach was the mainstay of treatment, and more potent drugs were administered in case patients were refractory to, or intolerant of, first-line therapies.[24] In general, the strategies for treating EOUC did not differ from those for treating N-EOUC in Korea.[13] Patients were followed up regularly, usually every 1 to 3 months, depending on their conditions and based on the physicians' discretion. Endoscopy timing and interval were determined for each patient at the physicians' discretion.

4. Statistical analysis

Continuous variables are showed as medians and interquartile ranges (IQRs), whereas categorical parameters are showed as numbers and percentages. The t-tests were

performed to compare continuous variables, and the chi-square tests were used to compare categorical variables. Cumulative risks of medication use for UC, clinical remission, disease relapse, proximal disease extension, hospitalization, and colectomy were calculated with the Kaplan-Meier methods, and the values were compared between groups with the log-rank tests. Multivariate Cox regression analyses with the stepwise selection methods were used to investigate significant risk factors of the cumulative probabilities of proximal disease extension, hospitalization, and colectomy and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

One thousand and thirteen patients who were diagnosed with UC between January 1986 and December 2015 were included in this study.[4] After excluding 48 patients who were diagnosed with UC before the age of 18 years, we included a total of 99 (10.3%) and 866 (89.7%) patients who were diagnosed with EOUC and N-EOUC, respectively. The baseline features of patients with EOUC and N-EOUC are shown in Table 1. The proportion of men was significantly higher in the EOUC group than in the N-EOUC group (p=0.009) (Table 1). Furthermore, the proportion of current smokers was lower in the EOUC group than in the N-EOUC group (p<0.001), and the duration of follow-up after the diagnosis of UC was shorter in the EOUC group than in the N-EOUC group (p<0.001) (Table 1).

2. Medical treatment

At diagnosis and/or during the follow-up of median 89.5 months (IQR, 54.3 to 125.9 months), systemic corticosteroids (excluding topical corticosteroid therapy), thiopurines, and anti-tumor necrosis factor (TNF) agents were administered to 30.3%, 12.1%, and 8.1% of patients with EOUC, respectively (Table 1). The median intervals from UC diagnosis to medication initiation were 13.5 months (IQR, 0.5 to 26.1 months) for corticosteroids, 24.4 months (IQR, 10.7 to 60.1 months) for thiopurines, and 36.7 months (IQR, 28.2 to 47.8 months) for anti-TNFs in patients with EOUC. The cumulative risks of medication initiation at 1, 5, and 10 years after UC diagnosis were 15.3%, 32.2%, and 32.2%, respectively, for corticosteroids; 4.1%, 9.9%, and 13.4%, respectively, for thiopurines; and 0.0%, 6.5%, and 8.0%, respectively, for anti-TNFs in patients with EOUC (Fig. 1). The cumulative risks of medication use were not different between EOUC and N-EOUC groups (p=0.091 for corticosteroids, p=0.794 for thiopurines, and p=0.095 for anti-TNFs) (Fig. 1). Fourteen patients (1.6%) in N-EOUC and none in EOUC received cyclosporine during the study period. One patient (0.1%) in N-EOUC and none in EOUC received vedolizumab during the follow-up.

Table 1. Baseline Characteristics of the Study Patients

Clinical characteristics	Total	EOUC	N-EOUC	p-value
No. of patients	965 (100)	99 (10.3)	866 (89.7)	
Male sex	514 (53.3)	65 (65.7)	449 (51.8)	0.009
Age at UC diagnosis, yr	37 (28–49)	66 (62–68)	35 (27–44)	<0.001
Interval from onset to UC diagnosis, mo	2.8 (1.0–9.4)	2.0 (0.7–7.0)	3.0 (1.1–9.8)	0.477
Smoking status at UC diagnosis				<0.001
Non-smoker	508 (52.6)	47 (47.5)	461 (53.2)	
Former smoker	161 (16.7)	36 (36.4)	125 (14.4)	
Current smoker	153 (15.9)	8 (8.1)	145 (16.7)	
Disease extent at UC diagnosis				0.411
Proctitis	536 (55.5)	61 (61.6)	475 (54.8)	
Left-sided colitis	216 (22.4)	18 (18.2)	198 (22.9)	
Extensive colitis	213 (22.1)	20 (20.2)	193 (22.3)	
Family history	44 (4.6)	5 (5.1)	39 (4.5)	0.805
Duration of follow-up, mo	104.5 (60.3–168.7)	89.5 (54.3–125.9)	106.2 (62.0–172.4)	<0.001
Ever use of medications				
Systemic corticosteroids	377 (39.1)	30 (30.3)	347 (40.1)	0.059
Thiopurines	124 (12.8)	12 (12.1)	112 (12.9)	0.819
Anti-TNFs	56 (5.8)	8 (8.1)	48 (5.5)	0.306

Data are presented as number (%) or median (interquartile range).
EOUC, elderly-onset ulcerative colitis; N-EOUC, non-EOUC; UC, ulcerative colitis; TNF, tumor necrosis factor.

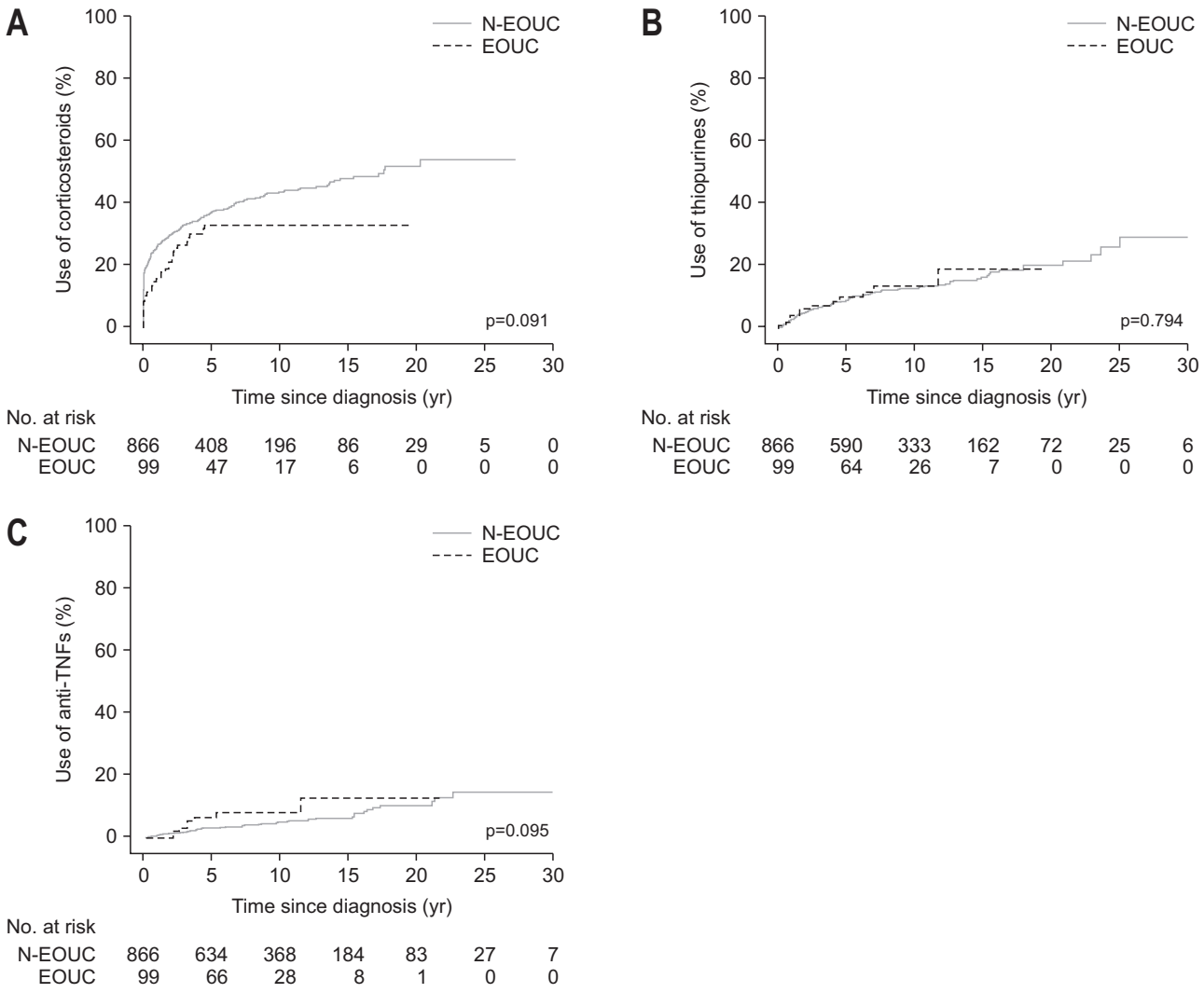

Fig. 1. Cumulative risk of medication use in patients with elderly-onset ulcerative colitis (EOUC) and non-EOUC (N-EOUC): (A) corticosteroids, (B) thiopurines, and (C) anti-tumor necrosis factor (TNF) agents.

3. Remission

Among the 99 patients in the EOUC group, 87 patients (87.9%) achieved clinical remission. Remission was not reported in seven patients (7.1%). The cumulative rates of remission at 1, 5, and 10 years after UC diagnosis were 80.4%, 93.0%, and 93.0%, respectively. The cumulative remission rates were not different between the EOUC and N-EOUC patients (p=0.348).

4. Proximal disease extension on endoscopy

In EOUC, endoscopic disease extent at UC diagnosis was divided as proctitis (E1) in 61 cases (61.6%), left-sided colitis (E2) in 18 cases (18.2%), and extensive colitis (E3) in 20 cases (20.2%). The proportions of patients with E1, E2, and E3 at UC diagnosis were not different between the EOUC and N-EOUC patients (p=0.199, p=0.290, and p=0.636, respectively). Of 79 cases with EOUC with E1 or E2 at UC diagnosis, proximal disease extension was identified in 17 (21.5%; 16 cases with E1 and one patient with E2) patients, with a median time to proximal extension of 36.6 months (IQR, 23.0 to 61.3 months). The cumulative risks of proximal disease extension after 1, 10, and 15 years were 16.5%, 22.4%, and 31.8% respectively, in 79 patients with EOUC with E1 or E2 at UC diagnosis (Fig. 2A). The cumulative risks of proximal disease extension were comparable between the EOUC and N-EOUC groups (p=0.351) (Fig. 2A). Even after controlling the differences of baseline characteristics such as sex and smoking status in a multivariate Cox regression analysis, EOUC was not a significant predictive factor for proximal disease extension (HR, 0.699; 95% CI, 0.422 to 1.156; p=0.163). In patients with EOUC, multivariate analysis showed that corticosteroid use at UC diagnosis (HR, 6.216; 95% CI, 1.314 to 28.826) was an independent predictor of proximal disease extension (Table 2).

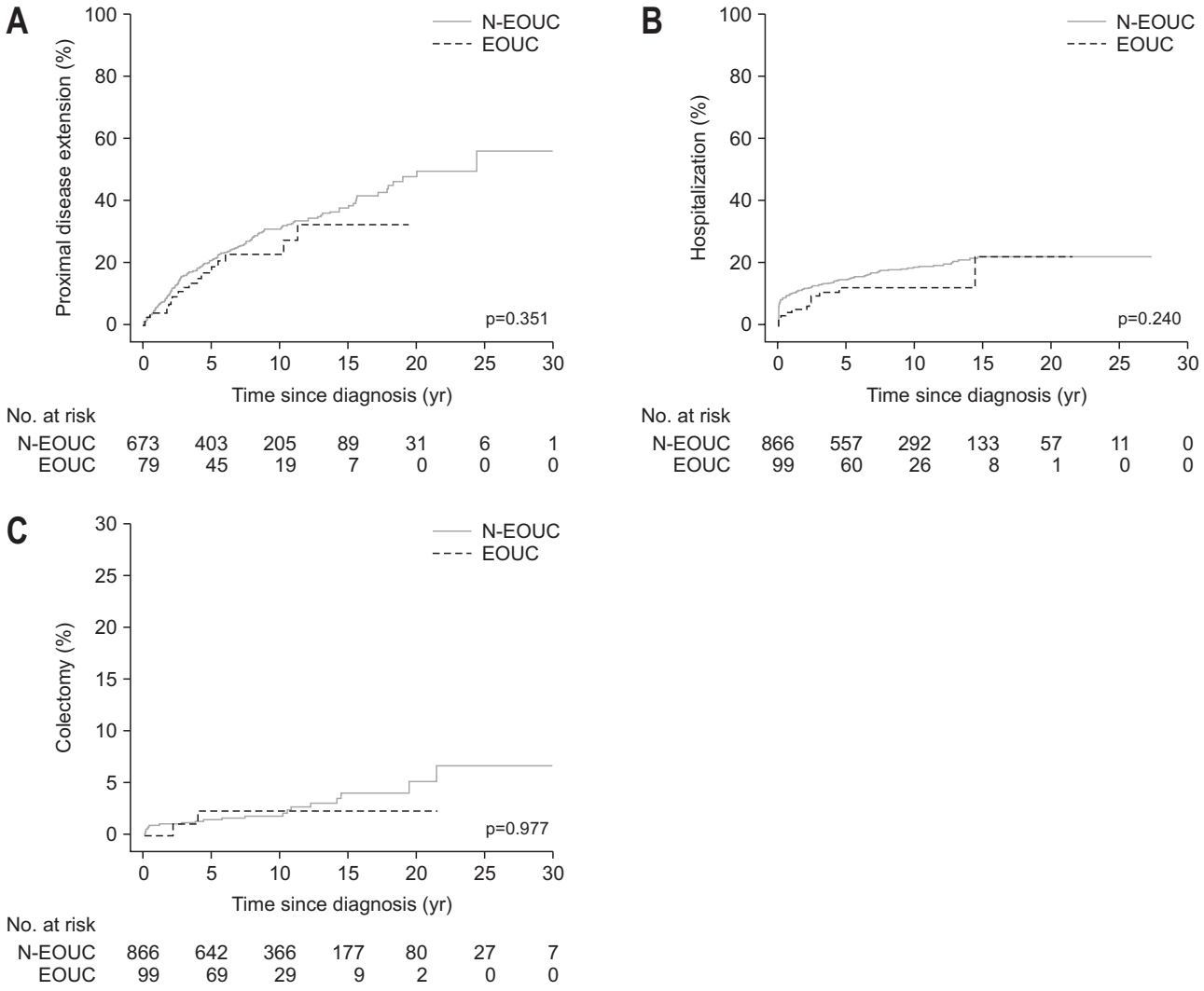

Fig. 2. Cumulative risk of disease outcomes in patients with elderly-onset ulcerative colitis (EOUC) and non-EOUC (N-EOUC): (A) proximal disease extension, (B) hospitalization, and (C) colectomy.

5. Hospitalization

Among the 99 patients with EOUC, a total of 12 patients (12.1%) had histories of at least one hospitalization that required the administration of systemic steroids, immunomodulators, or anti-TNFs or colectomy at UC diagnosis or during the follow-up. The median number of hospitalizations per patient was 1 (IQR, 1 to 2), and the median interval from UC diagnosis to the first hospitalization was 29.3 months (IQR, 14.9 to 55.6 months). The cumulative risks of hospitalization at 1, 5, and 10 years after diagnosis were 5.1%, 11.9%, and 11.9%, respectively (Fig. 2B). The cumulative risk of hospitalization was not different between the EOUC and N-EOUC patients (p=0.240) (Fig. 2B). Even after controlling the differences of baseline characteristics such as sex and smoking status in a multivariate Cox regression analysis, EOUC was not a significant predictive factor for hospitalization (HR, 0.688; 95% CI, 0.379 to 1.251; p=0.220). In patients with EOUC, multivariate analysis showed that corticosteroid use at UC diagnosis (HR, 11.241; 95% CI, 3.027 to 41.742) was an independent predictor of hospitalization (Table 3).

6. Colectomy

Of the 99 patients with EOUC, two cases (2.0%) underwent colectomy during the follow-up. The reasons for colectomy were medical refractoriness despite maximum medical therapy in one patient (total colectomy with permanent ileostomy) and perforation in one patient (subtotal colectomy with Hartmann closure). The cumulative risks of colectomy at 1, 5, 10, and 20 years after UC diagnosis were 0.0%, 2.3%, 2.3%, and 2.3%, respectively (Fig. 2C). The cumulative risk of colectomy was comparable between the EOUC and N-EOUC groups (p=0.977) (Fig. 2C). Even after controlling the differences of baseline characteristics

Table 2. Factors for Proximal Disease Extension in Patients with Elderly-Onset Ulcerative Colitis

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sex				
Female	Reference		Not included	
Male	0.752 (0.286–1.977)	0.563		
Smoking status at UC diagnosis				
Non-smoker	Reference		Not included	
Former smoker	0.000	0.986		
Current smoker	0.772 (0.285–2.090)	0.610		
Family history of IBD				
No	Reference		Not included	
Yes	0.825 (0.109–6.256)	0.852		
Disease extent at UC diagnosis				
Proctitis	Reference		Reference	
Left-sided colitis	0.198 (0.026–1.498)	0.117	0.164 (0.021–1.271)	0.084
Use of corticosteroids at UC diagnosis				
No	Reference		Reference	
Yes	4.409 (0.989–19.662)	0.052	6.216 (1.341–28.826)	0.020

CI, confidence interval; UC, ulcerative colitis; IBD, inflammatory bowel disease.

Table 3. Factors for Hospitalization in Patients with Elderly-Onset Ulcerative Colitis

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sex				
Female	Reference		Not included	
Men	0.523 (0.168–1.625)	0.262		
Smoking status at UC diagnosis				
Non-smoker	Reference		Not included	
Former smoker	0.649 (0.080–5.263)	0.685		
Current smoker	0.519 (0.138–1.959)	0.333		
Family history of IBD				
No	Reference		Not included	
Yes	0.045 (0.000–1,672.382)	0.563		
Disease extent at UC diagnosis				
Proctitis	Reference		Not included	
Left-sided colitis	0.615 (0.074–5.150)	0.615	0.501 (0.059–4.272)	0.527
Extensive colitis	3.340 (0.974–11.456)	0.055	1.844 (0.490–6.935)	0.365
Use of corticosteroids at UC diagnosis				
No	Reference		Reference	
Yes	13.406 (3.990–45.037)	<0.001	11.241 (3.027–41.742)	<0.001

CI, confidence interval; UC, ulcerative colitis; IBD, inflammatory bowel disease.

such as sex and smoking status in a multivariate Cox regression analysis, EOUC was not a significant predictive factor for colectomy (HR, 0.888; 95% CI, 0.203 to 3.887; p=0.875). In EOUC, no significant independent predictor of colectomy was identified in the multivariate Cox regression analysis (Table 4).

DISCUSSION

In the present study, we investigated the long-term outcomes of EOUC in Korea using the well-established population-based cohort. The most notable finding of the current population-based study is that the cumulative rates of colectomy did not differ significantly between patients with EOUC and N-EOUC (p=0.817). This result seems comparable to the results of previous Western population-based studies.[7,17,19,25] Meanwhile, referral center-based studies from both Western and Eastern countries showed higher cumulative rates of colectomy in the EOUC group than in the N-EOUC group.[12-14] Also, recent multicenter studies from Hong Kong showed that EO-IBD patients had

Table 4. Factors for Colectomy in Patients with Elderly-Onset Ulcerative Colitis

Factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sex				
Female	Reference		Not included	
Male	0.535 (0.033–8.559)	0.659		
Smoking status at UC diagnosis				
Non-smoker	Reference		Not included	
Former smoker	1.380 (0.085–22.100)	0.820		
Current smoker	0.000	0.994		
Family history of IBD				
No	Reference		Not included	
Yes	21.754 (0.000–2.740E+13)	0.828		
Disease extent at UC diagnosis				
Proctitis	Reference		Not included	
Left-sided colitis	0.336 (0.021–5.366)	0.440		
Extensive colitis	0.000	0.987		
Use of corticosteroids at UC diagnosis				
No	Reference		Reference	
Yes	10.856 (0.675–174.542)	0.092	5.822 (0.134–253.684)	0.360
Ever use of medications				
Systemic corticosteroids	2.121 (0.133–33.920)	0.595	Not included	
Thiopurines	7.387 (0.461–118.274)	0.158	2.606 (0.060–113.127)	0.619
Anti-TNFs	0.043 (0.000–126,027,425.000)	0.778	Not included	

CI, confidence interval; UC, ulcerative colitis; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

a higher risk of infection, cancer, and hospitalization.[15,16] Although the cause of this discrepancies among results is unclear, differences in the study design (referral center-based vs population-based) may play a critical role.

Regarding medical treatment, the cumulative rates of the initiation of medications, including corticosteroids, thiopurines, and anti-TNFs, were similar between the two groups in our study. These results are in contrast with those of previous studies from Western countries, which reported that the cumulative use of steroids is comparable between the EOUC and N-EOUC groups, whereas immunomodulators such as thiopurines and biologics are used less frequently in the EOUC group than in the N-EOUC group.[7,17,25,26] The reason for this difference in the pattern of medication use between Korean and Western patients with EOUC is unclear. It may be partly explained by the differences in the attitudes of physicians and patients to chronic medication exposure because immunosuppressants are usually avoided for long-term use in elderly patients due to the increased risk of side effects, such as infection and malignancies.[10,11] Additionally, cultural preferences in Asian regions, such as the use of Eastern medicine or Confucianism, may contribute to the difference in results regarding medical therapy between this study and Western studies.[27]

It is likely that the comparable cumulative rates of the use of disease-modifying drugs, including immunomodulators or anti-TNFs, between patients with EOUC and N-EOUC may be a contributing factor to the comparable colectomy rate between the two groups; this is in contrast to the higher rate of colectomy in patients with EOUC than in patients with N-EOUC, as demonstrated by previous hospital-based studies including our previous study.[12,13] To date, there have been conflicting data regarding age as a sole significant factor for the risk of opportunistic infection in patients with IBD receiving immunosuppressants. Although EOUC usually tends to be treated conservatively with the consideration of frequent comorbidities, in a recent post hoc analysis of the randomized evaluation of an algorithm for Crohn's treatment, the strategy of early combined immunosuppression was equally effective and safe in older and younger patients, compared to conventional management; this strategy decreased the risks of surgery, hospitalization, and disease-related complications.[28] Additionally, according to a recent pooled analysis of data from randomized trials, older patients with UC had no incremental risk of serious adverse events attributable to anti-TNF therapy compared to younger patients.[29] Moreover, a recent study reported that frailty, independent of age, was related with an increased infection risk after the administration of anti-TNF and immunomodulatory agents in patients with IBD, suggesting frailty rather than chronological age may provide a more comprehensive assessment of the infection risk.[30]

Another important finding of the current study is that

corticosteroid use at diagnosis was associated with poor disease outcomes, including proximal disease extension and hospitalization, in patients with EOUC. This finding seems comparable with the findings of previous Western studies, in which corticosteroid dependency or the use of corticosteroids was associated with poor disease outcomes of UC, such as high surgery rates.[18,25] According to a recent meta-analysis of Western population-based studies, more extensive disease and corticosteroid use were associated with an increased risk of colectomy in EOUC.[17] However, the predictors associated with colectomy were not identified in this study probably due to the small number of events (i.e., only two cases underwent colectomy during the follow-up). As described in our previous report, Korean patients with UC showed a lower colectomy rate than Western patients.[21]

The current study has the following strength: this study used a population-based design in a well-established administrative region, which enabled us to include unselected patients representing the entire disease spectrum. Moreover, this study assessed the natural history of EOUC in a non-Caucasian population-based cohort; our findings may be used to develop evidence-based guidelines for the management of EOUC, specifically in Asian populations.

However, our study has some limitations. First, we could not investigate the impact of baseline disease activity on the UC outcome because data on UC disease activity at diagnosis and baseline laboratory results were not collected. Instead, we used the corticosteroid use at UC diagnosis as a surrogate marker of baseline disease activity. Second, we did not collect data on the comorbidities including malignancies and infections that may affect UC outcomes in this study. However, unlike the previous studies that reported a worse prognosis of EOUC than of N-EOUC,[12-14] the results of the present study may suggest that EOUC does not have an aggressive disease course compared to that of N-EOUC despite the possibility of a higher burden of comorbidities in patients with EOUC than in those with N-EOUC. Third, whether the findings of this study can be generalized to other Asian populations remains unclear, considering that there are genotypic and phenotypical variations in IBD among Asian countries.[31] Lastly, we could not evaluate the causality between therapy patterns and disease outcomes, including colectomy, in EOUC in this analysis.

In conclusion, the natural course and outcomes of EOUC seem to be comparable to those of N-EOUC, along with similar rates of the use of medications, including corticosteroids and disease-modifying drugs, at a population level in Korea. Moreover, the risk factors for disease outcomes in the EOUC group seem comparable to those in the Western population. By understanding the long-term clinical course of EOUC, we can manage this subset of patients with UC more appropriately and in a timely manner.

CONFLICTS OF INTEREST

S.K.Y. received a research grant from Janssen Korea. The remaining authors disclose no conflicts.

J.P.I. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: S.H.P., S.K.J., J.H.L., B.D.Y., S.K.Y. Acquisition of data: S.H.P., K.H.R., Y.H.K., S.N.H., K.H.K., S.I.S., J.M.C., S.Y.P., S.K.J., J.H.L., H.P., J.S.K., J.P.I., H.Y., S.H.K., J.J., J.H.K., S.O.S., Y.K.K., B.D.Y., S.K.Y. Statistical analysis and interpretation of data: S.H.P., B.D.Y., S.K.Y. Drafting of the manuscript: S.H.P., S.K.J., J.H.L., S.K.Y. Critical revision of the manuscript for important intellectual content: S.K.Y. Study supervision: S.K.Y.

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