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Retrospective Cohort Study

Increased end-stage renal disease risk in patients with inflammatory bowel disease: A nationwide population-based study

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Abstract

AIM

To estimate the risk of end-stage renal disease (ESRD)

in patients with inflammatory bowel disease (IBD).

METHODS

From January 2010 to December 2013, patients with Crohn's disease (CD) and ulcerative colitis (UC) were identified, based on both the International Classification of Diseases, 10th revision (ICD-10) and the rare, intractable disease registration program codes from the National Health Insurance (NHI) database in South Korea. We compared 38812 patients with IBD to age- and sex-matched non-IBD controls with a ratio of 1:3. Patients newly diagnosed with ESRD were identified with the ICD-10 code.

RESULTS

During a mean follow-up of 4.9 years, ESRD was detected in 79 (0.2%) patients with IBD and 166 (0.1%) controls. The incidence of ESRD in patients with IBD was 0.42 per 1000 person-years. Patients with IBD had a significantly higher risk of ESRD than controls [adjusted hazard ratio (HR) = 3.03; 95% confidence interval (CI): 1.77-5.20; $P < 0.001$]. The incidences (per 1000 person-years) of ESRD were 0.51 in patients with CD and 0.13 in controls, respectively (adjusted HR = 6.33; 95%CI: 2.75-14.56; $P < 0.001$). In contrast, the incidence of ESRD was similar between the UC and control groups (0.37 vs 0.37 per 1000 person-years; adjusted HR = 2.01; 95%CI: 0.90-4.51; $P = 0.089$).

CONCLUSION

The risk of ESRD was elevated in patients with CD, but not UC. Patients with CD should be monitored carefully for signs of renal insufficiency.

Key words: Claims data; Inflammatory bowel disease; Crohn's disease; End-stage renal disease; Ulcerative colitis

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Core tip: In this nationwide population-based study, we demonstrated that incidence of end-stage renal disease (ESRD) is significantly higher in patients with inflammatory bowel disease (IBD) compared to age- and sex-matched controls without IBD. To the best of our knowledge, this population-based study was the first to determine the incidence and risks of ESRD in patients with IBD. The incidence of ESRD in patients with Crohn's disease (CD) was approximately 5 times higher compared to controls. Patients with CD are at a significant risk of developing ESRD regardless of age, sex, comorbidities. Our study provides new evidence for the association between ESRD and CD.

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INTRODUCTION

End-stage renal disease (ESRD), the final stage of chronic kidney disease (CKD), has emerged as one of the most important public health issues worldwide. Old age, diabetes mellitus (DM), hypertension, and hyperuricemia have been identified as traditional independent risk factors of ESRD^[1]. The prevalence of ESRD is expected to rise over the next several decades, due to the increasing proportion of individuals at risk of ESRD in the general population. The estimated number of patients that required renal replacement therapy worldwide was 2.618 million in 2010, and the number is expected to rise to 5.439 million in 2030^[2]. ESRD increases the risk of premature death, and incurs enormous socio-economic costs^[3]. Recently, patients with ESRD comprised less than 1% of the total Medicare population, but they consumed approximately 7% of the overall Medicare fee-for-service budget in the United States^[4].

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, relapsing, inflammatory disease that mainly involves the intestines^[5-7]. The prevalence of IBD continues to increase steadily in western countries, and the incidence is rapidly increasing in developing countries^[8-11]. Patients with IBD can develop various extra-intestinal manifestations (EIMs), which can lead to high morbidity, and occasionally, life-threatening consequences. Renal manifestations, including nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, and secondary amyloidosis, develop in 4%-23% of patients with IBD^[12]. Each of these conditions can induce renal insufficiency. Kidney injury may also result from dehydration, malnutrition, or medication side effects in patients with IBD^[12,13]. A few epidemiologic studies have reported incidences of renal insufficiency that ranged from 2.0% to 15.9% in patients with IBD^[14,15]. However, to date, the incidence and risk factors of ESRD have not been evaluated in patients with IBD, because ESRD is considered to be a very rare manifestation of IBD. Here, we conducted a nationwide population-based study to estimate the incidence and evaluate risk factors of ESRD in patients with IBD.

MATERIALS AND METHODS

Data source

This retrospective cohort study retrieved data from the National Health Insurance (NHI) database, which is provided by the Korean government. The NHI is a mandatory health insurance program that covers about 97% of the Korean population; the remaining 3% of the population is covered by medical aid. The NHI database

includes information on patient demographics, medical treatments, outpatient and inpatient care, disease diagnoses, prescriptions, and procedure records. NHI data on individuals are assigned non-identifiable codes to protect personal information^[16]. In 2006, the NHI established a registration program for rare, intractable diseases (RIDs), including IBD and ESRD, to identify patients that required enhanced reimbursement for the medical costs associated with these diseases. To qualify for enrollment in this special co-payment program, patients had to meet the diagnostic criteria provided by the NHI for each RID, and the assessments had to be approved by specialized physicians. The diagnostic codes were defined according to codes from the International Classification of Diseases, 10th revision (ICD-10), and a special code (V code) was assigned in the RID database^[17]. To be eligible for the RID program and assigned a V code, patients with IBD had to meet specific diagnostic criteria, including clinical features, endoscopic findings, and histologic findings. Previous studies have validated the accuracy of the RID database for both CD and UC diagnoses^[17,18].

Study population and patient identification

This study included all patients with IBD in the NHI database that were assigned both the V code and the ICD-10 code, from January 2010 to December 2013. The NHI and RID databases included patients with CD (registration code: V130, ICD-10 code: K50) and UC (registration code: V131; ICD-10 code: K51). The IBD cohort was divided into an incidence group and a prevalence group. The IBD incidence group included all patients who were newly identified through both the ICD-10 and V codes for CD and UC, from January 2010 to December 2013. These patients had no history of CD or UC from January 2005 until the inclusion date (index day) of the study. The IBD prevalence group included all patients who were formerly assigned IBD codes, from 2005 to index day, and received reimbursements for IBD during the 2010 to 2013 period.

To assess the diagnostic accuracy of IBD defined with the V code and ICD-10 codes, the medical records of all patients with IBD were reviewed retrospectively at Seoul National University Hospital (SNUH), a tertiary referral hospital in Korea. A total of 830 patients with IBD were enrolled at SNUH, based on both ICD-10 code and V code assignments, from January 2010 to December 2013. The diagnostic sensitivities for CD and UC were 94.5% (312/330) and 96.4% (482/500), respectively. Age- and sex-matched individuals without IBD were randomly selected and included in the study at a ratio of 3 controls for each patient with IBD (3:1).

Data collection and study endpoints

We collected data on patient demographics (age, sex, place of residence, and income level) and on the medications used for IBD treatment, including 5-aminosalicylic acid (ASA), corticosteroids, immunomodulators (azathioprine/6-mercaptopurine and methotrexate), and anti-tumor

necrosis factor (TNF)- α agents (infliximab, adalimumab and golimumab). Medication use was defined as all relevant medications prescribed within 1 year of the diagnosis of IBD. We also collected information on comorbidities identified with ICD-10 codes, including hypertension (ICD-10 codes: I10-13 and I15, and medications for treating hypertension), DM (E11-14, and medications for treating DM), dyslipidemia (E78, and medications for treating dyslipidemia), congestive heart failure (I50), ischemic heart disease (I20-I25), hyperuricemia, and gout (E79 and M10). The definitions of these comorbidities were validated previously^[19]. The metabolically healthy condition was defined as the absence of DM, hypertension, and dyslipidemia. An underlying disease was defined as the presence of at least one of the following: DM, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, hyperuricemia, and gout.

The primary endpoint was newly diagnosed ESRD during follow-up. ESRD was detected with the combination of an ICD-10 code (N18-19, Z49, Z94.0, and Z99.2) and a V code assigned to patients with CKD that required hemodialysis (V001), peritoneal dialysis (V003), or a kidney transplantation (V005), as defined previously^[19]. All patients that underwent dialysis or a kidney transplantation were enrolled in the RID program; therefore, we could identify and analyze data for all patients with ESRD in the study population. Both the IBD cohort and the matched control cohort were followed-up for the development of ESRD until December 2015. During follow-up, patients without newly developed ESRD were censored on the last day of follow-up or the date of death.

Statistical analysis

Statistical analyses were performed with the R program, version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>) and SAS, version 9.2 (SAS Institute Inc., Cary, NC, United States) for Windows. Random selection of age- and sex-matched controls was performed with the SAS algorithm. Data for continuous variables are presented as the mean and standard deviation. Data for categorical variables are presented as numbers and percentages. Differences in baseline characteristics and comorbidities between the IBD cohort and control individuals were analyzed with independent *t*-tests and χ^2 tests, as appropriate. Incidences of ESRD and mortality were calculated by dividing the number of events by 1000 person-years of follow up for each group. Cox proportional hazard regression models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of ESRD and the mortality, after adjusting for covariates, in patients with IBD compared to controls. The cumulative incidences of ESRD were compared between groups with the Kaplan-Meier method and the log-rank test. Subgroups defined by age, sex, metabolic health, and underlying diseases were analyzed with the test for

Table 1 Baseline characteristics of the study population of patients without (control) or with inflammatory bowel disease *n* (%)

	IBD			CD			UC		
	Non-IBD control (<i>n</i> = 116436)	IBD cohort (<i>n</i> = 38812)	<i>P</i> value	Non-CD control (<i>n</i> = 37755)	CD cohort (<i>n</i> = 12585)	<i>P</i> value	Non-UC control (<i>n</i> = 78681)	UC cohort (<i>n</i> = 26227)	<i>P</i> value
Age, yr ¹	40.0 ± 16.7	40.0 ± 16.7	-	30.7 ± 14.6	30.7 ± 14.6	-	44.4 ± 15.8	44.4 ± 15.8	-
< 15	3639 (3.1)	1213 (3.1)		2562 (6.8)	854 (6.8)		1077 (1.4)	359 (1.4)	
15-39	56679 (48.7)	18893 (48.7)		26577 (70.4)	8859 (70.4)		30102 (38.3)	10034 (38.3)	
≥ 40	56118 (48.2)	18706 (48.2)		8616 (22.8)	2872 (22.8)		47502 (60.4)	15834 (60.4)	
Male gender	71040 (61.0)	23680 (61.0)	-	26451 (70.1)	8817 (70.1)	-	44589 (56.7)	14863 (56.7)	-
Rural residence	62045 (53.3)	19312 (49.8)	< 0.001	20043 (53.1)	6163 (49.0)	< 0.001	42002 (53.4)	13149 (50.1)	< 0.001
Lowest income 20% ²	33008 (28.4)	9316 (24.0)	< 0.001	10705 (28.4)	3229 (25.7)	< 0.001	22303 (28.6)	6087 (23.2)	< 0.001
DM	5786 (5.0)	1612 (4.2)	< 0.001	845 (2.3)	280 (2.2)	0.931	4941 (6.3)	1332 (5.1)	< 0.001
Hypertension	14958 (12.9)	4494 (11.6)	< 0.001	2294 (6.1)	665 (5.3)	0.001	12664 (16.1)	3829 (14.6)	< 0.001
Dyslipidemia	8620 (7.4)	2718 (7.0)	0.009	1358 (3.6)	376 (3.0)	0.001	7262 (9.2)	2342 (8.9)	0.145
Congestive heart failure	781 (0.7)	356 (0.9)	< 0.001	119 (0.3)	85 (0.7)	< 0.001	662 (0.8)	271 (1.0)	0.004
Ischemic heart disease	4028 (3.5)	1747 (4.5)	< 0.001	616 (1.6)	381 (3.0)	< 0.001	3412 (4.3)	1366 (5.2)	< 0.001
Gout and/or hyperuricemia	1552 (1.3)	650 (1.7)	< 0.001	320 (0.9)	211 (1.7)	< 0.001	1232 (1.6)	439 (1.7)	< 0.001
Medications for IBD									
5-ASA	121 (0.1)	36288 (93.5)	< 0.001	32 (0.1)	11233 (89.3)	< 0.001	89 (0.1)	25055 (95.5)	< 0.001
Corticosteroids	0 (0.0)	22284 (57.4)	< 0.001	0 (0.0)	7382 (58.7)	< 0.001	0 (0.0)	14902 (56.8)	< 0.001
Immunomodulators	0 (0.0)	10356 (26.7)	< 0.001	0 (0.0)	6982 (55.5)	< 0.001	0 (0.0)	3374 (12.9)	< 0.001
Anti-TNF-α	0 (0.0)	2103 (5.4)	< 0.001	0 (0.0)	1659 (13.2)	< 0.001	0 (0.0)	444 (1.7)	< 0.001
Follow-up period, yr ¹	4.9 ± 1.3	4.9 ± 1.3	0.337	4.9 ± 1.3	4.9 ± 1.3	0.004	4.9 ± 1.3	4.9 ± 1.3	0.418

¹Mean ± SD; ²Defined as patients whose income was in the bottom 20%. ASA: Aminosalicic acid; CD: Crohn's disease; DM: Diabetic mellitus; IBD: Inflammatory bowel disease; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

interaction. A *P*-value < 0.05 was considered statistically significant.

Ethical considerations

This study performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was approved by the SNUH Institutional Review Board (H-1703-107-840). All personal information from the NIH database was encrypted and all data were anonymous; therefore, we were not required to obtain informed consent from the study participants.

RESULTS

Baseline characteristics of the study population

From January 2010 to December 2013, a total of 38812 patients with IBD were enrolled in the IBD cohort (mean age 40.0 ± 16.7 years and 61.0% males). Of these, 16606 patients (42.8%) were included in the IBD incidence group. The IBD cohort comprised 12585 patients with CD and 26227 patients with UC. The control group comprised 116436 age- and sex-matched subjects without IBD. Compared to the control group, the IBD cohort had significantly lower proportions of rural residents (*P* < 0.001) and individuals with incomes in the bottom 20% (*P* < 0.001). Moreover, compared to controls, the IBD cohort had significantly lower prevalences of DM (4.2% vs 5.0%; *P* < 0.001), hypertension (11.6% vs 12.9%; *P* < 0.001), and dyslipidemia (7.0% vs 7.4%; *P* = 0.009), and higher prevalences of congestive heart failure (0.9% vs 0.7%; *P* < 0.001), ischemic heart disease (4.5% vs 3.5%;

P < 0.001), and gout and hyperuricemia (1.7% vs 1.3%; *P* < 0.001). The CD and UC groups were not significantly different from controls in the trends of covariates, except for DM and dyslipidemia. Among the medications prescribed for IBD, 5-ASA, corticosteroids, immunomodulators, and anti-TNF-α agents were prescribed to 36288 (93.5%), 22284 (57.4%), 10356 (26.7%), and 2103 (5.4%) patients with IBD, respectively. The immunomodulators and anti-TNF-α agents were used more frequently by patients with CD than by patients with UC (Table 1).

Development of ESRD in patients with inflammatory bowel diseases

During a mean follow-up period of 4.9 years, ESRD was newly diagnosed in 79 (0.2%) patients with IBD and in 166 (0.1%) control individuals. Among the patients of ESRD, 238 patients underwent dialysis and 7 patients underwent kidney transplantation. Overall, the incidence of ESRD was significantly higher in the IBD cohort than in controls (0.42 vs 0.29 per 1000 person-years; crude HR = 1.43; 95%CI: 1.09-1.87; *P* = 0.009; Table 2 and Figure 1A). The incidences of ESRD were 0.38 and 0.49 in the IBD prevalence and IBD incidence groups, respectively. The ESRD incidence was significantly higher in the IBD cohort compared to controls, after multivariate adjustments for age, sex, place of residence, income, comorbidities and medication use (adjusted HR = 3.03; 95%CI: 1.77-5.20; *P* < 0.001; Table 2). The ESRD incidence (per 1000 person-years) was 0.51 in patients with CD and 0.13 in controls (adjusted HR = 6.33; 95%CI: 2.75-14.56; *P* < 0.001). Among patients with CD in both the incident and prevalent CD groups, the

Table 2 Incidence and risk of end-stage renal disease in patients with inflammatory bowel diseases

	Total No. (n)	ESRD cases (n)	Person-years	ESRD incidence (per 1000 person-years)	Crude HR (95%CI)	P value	Model 1 ¹ HR (95%CI)	P value	Model 2 ² HR (95%CI)	P value	Model 3 ³ HR (95%CI)	P value
Total IBD												
Non-IBD control	116436	166	568575	0.29	1 (reference)	0.009	1 (reference)	0.009	1 (reference)	< 0.001	1 (reference)	< 0.001
IBD cohort	38812	79	189245	0.42	1.43 (1.09-1.87)		1.43 (1.09-1.87)		1.67 (1.27-2.18)		3.03 (1.77-5.20)	
IBD subgroup						0.013		0.004		< 0.001		< 0.001
Non-IBD control	116436	166	568575	0.29	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Incident IBD group	16606	32	65646	0.49	1.71 (1.17-2.50)		1.89 (1.29-2.73)		1.72 (1.17-2.52)		3.06 (1.71-5.47)	
Prevalent IBD group	22206	47	123600	0.38	1.29 (0.93-1.78)		1.23 (0.89-1.70)		1.63 (1.18-2.27)		3.01 (1.67-5.43)	

¹Model 1: adjusted for age and sex; ²Model 2: adjusted for model 1 + place of residence, income, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, and gout and/or hyperuricemia; ³Model 3: adjusted for model 2 + medication use (5-aminosalicylic acid, corticosteroids, immunomodulators, and anti-tumor necrosis factor -α agents). CI: Confidence interval; ESRD: End-stage renal disease; HR: Hazard ratio; IBD: Inflammatory bowel disease; No: Number.

Table 3 Incidence and risk of end-stage renal disease in patients with Crohn's disease and ulcerative colitis

	Total No. (n)	ESRD cases (n)	Person-years	ESRD incidence (per 1000 person-years)	Crude HR (95%CI)	P value	Model 1 ¹ HR (95%CI)	P value	Model 2 ² HR (95%CI)	P value	Model 3 ³ HR (95%CI)	P value
Total CD												
Non-CD control	37755	24	184988	0.13	1 (reference)	< 0.001	1 (reference)	< 0.001	1 (reference)	< 0.001	1 (reference)	< 0.001
CD cohort	12585	31	61189	0.51	3.90 (2.29-6.65)		4.00 (2.35-6.82)		3.98 (2.31-6.85)		6.33 (2.75-14.56)	
CD subgroup						< 0.001		< 0.001		< 0.001		< 0.001
Non-CD control	37755	24	184988	0.13	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Incident CD group	5586	14	21836	0.64	4.92 (2.53-9.57)		5.18 (2.66-10.07)		4.21 (2.12-8.35)		6.30 (2.56-15.26)	
Prevalent CD group	6999	17	39353	0.43	3.34 (1.79-6.23)		3.37(1.81-6.29)		3.81 (2.03-7.16)		6.38 (2.47-16.47)	
Total UC						0.941		0.961		0.307		0.089
Non-UC control	78681	142	383587	0.37	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
UC cohort	26227	48	128056	0.37	1.01 (0.73-1.40)		1.01 (0.73-1.40)		1.22 (0.88-1.70)		2.01 (0.90-4.51)	
UC subgroup						0.821		0.821		0.513		0.235
Non-UC control	78681	142	383587	0.37	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Incident UC group	11020	18	43810	0.41	1.14 (0.70-1.87)		1.27 (0.77-2.08)		1.19 (0.73-1.96)		1.99 (0.83-4.80)	
Prevalent UC group	15207	30	84247	0.36	0.95 (0.64-1.41)		0.90 (0.61-1.33)		1.24 (0.83-1.84)		2.03 (0.87-4.72)	

¹Model 1: adjusted for age and sex; ²Model 2: adjusted for model 1 + region, income, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, gout and/or hyperuricemia; ³Model 3: adjusted for model 2 + medication use (5-aminosalicylic acid, corticosteroids, immunomodulators, and anti-tumor necrosis factor -α agents). CD: Crohn's disease; CI: Confidence interval; ESRD: End-stage renal disease; HR: Hazard ratio; No: Number; UC: Ulcerative colitis.

ESRD incidence was also significantly higher compared to controls (Incident CD group: adjusted HR = 6.30; 95%CI: 2.60-15.26; $P < 0.001$; Prevalent CD group: adjusted HR = 6.38; 95%CI: 2.47-16.47; $P < 0.001$). In contrast, the ESRD incidence was not significantly different between the UC and control groups (adjusted HR = 2.01; 95%CI: 0.90-4.51; $P = 0.089$; Table 3; Figure 1B and C).

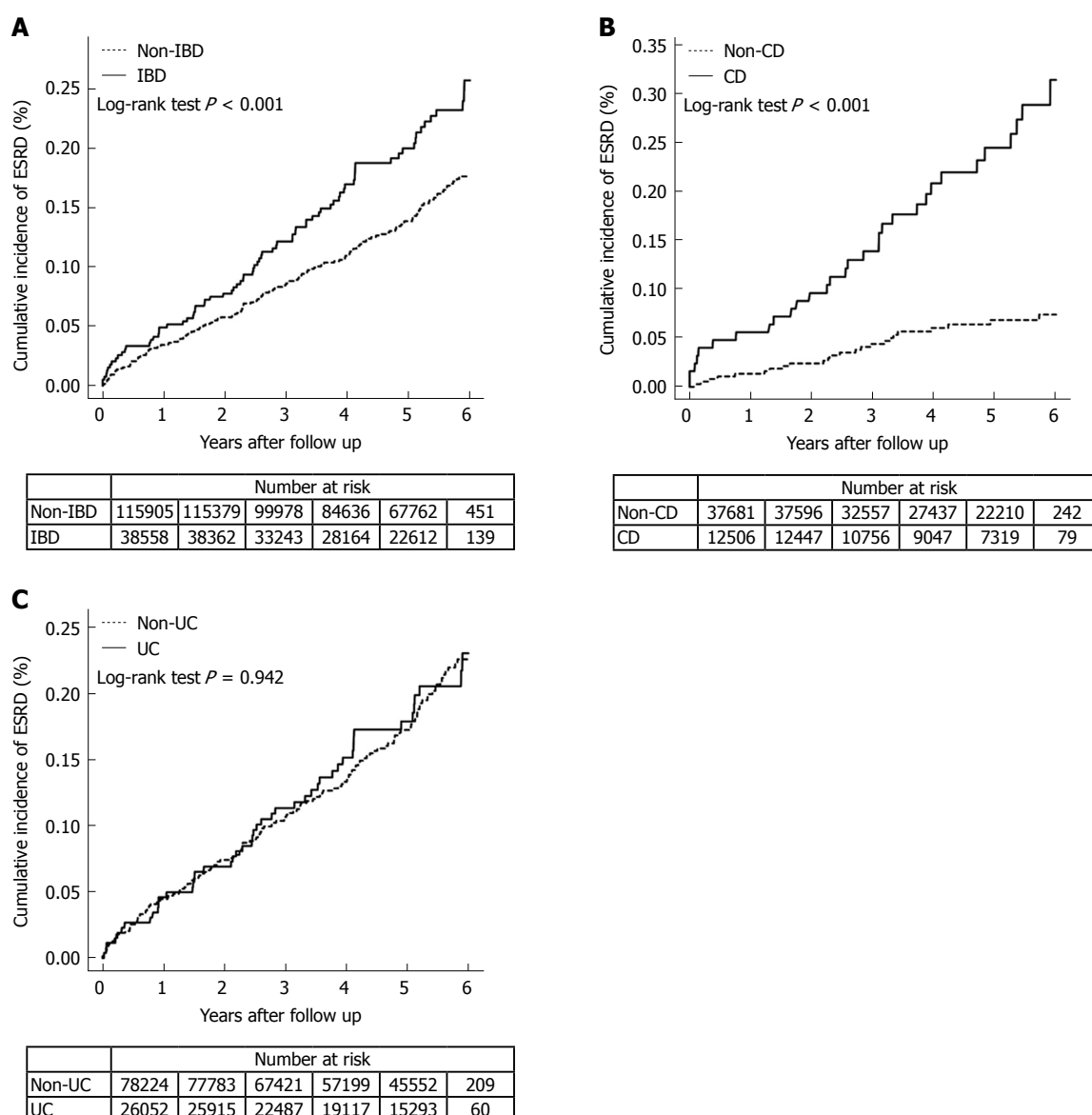


Figure 1 Kaplan-Meier plots show the cumulative incidence of end-stage renal disease in patients with inflammatory bowel disease. A: All patients with inflammatory bowel disease; B: Patients with Crohn's disease; C: Patients with ulcerative colitis. CD: Crohn's disease; ESRD: End-stage renal disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

Subgroup analysis

For the subgroup analysis, patients were dichotomized according to age, sex, and comorbidities. We found that, regardless of age, sex, and comorbidities, all patients with CD had a significantly higher risk of developing ESRD than controls. Moreover, the impact of CD on developing ESRD was more prominent among patients younger than 40 years old (adjusted HR: 8.24 vs 3.33; interaction $P = 0.198$) and patients that were metabolically healthy (adjusted HR: 10.07 vs 3.13; interaction $P = 0.074$; Figure 2A). In contrast, patients with UC showed no significant differences in the risk of developing ESRD compared to the control subgroups of sex and comorbidities. However, patients with UC that were younger than 40 years old had a higher risk of developing ESRD than those older than 40 years old (adjusted HR: 2.85 vs 1.07; interaction $P = 0.118$;

Figure 2B).

Development of ESRD according to medication use

Among patients with IBD, those with CD that were treated with 5-ASA had a significantly lower ESRD incidence than those with CD treated without 5-ASA (0.40 vs 1.68 per 1000 person-years; adjusted HR = 0.43; 95%CI: 0.19-0.99; $P = 0.048$). The ESRD incidence was not significantly different between patients treated with or without corticosteroids, immunomodulators, or anti-TNF- α agents (Supplementary Table 1)

Inflammatory bowel disease as a risk factor for overall mortality

The overall mortality rate was higher in IBD cohort compared to controls, but there was no statistically significant difference (4.76 vs 4.48 per 1000 person-

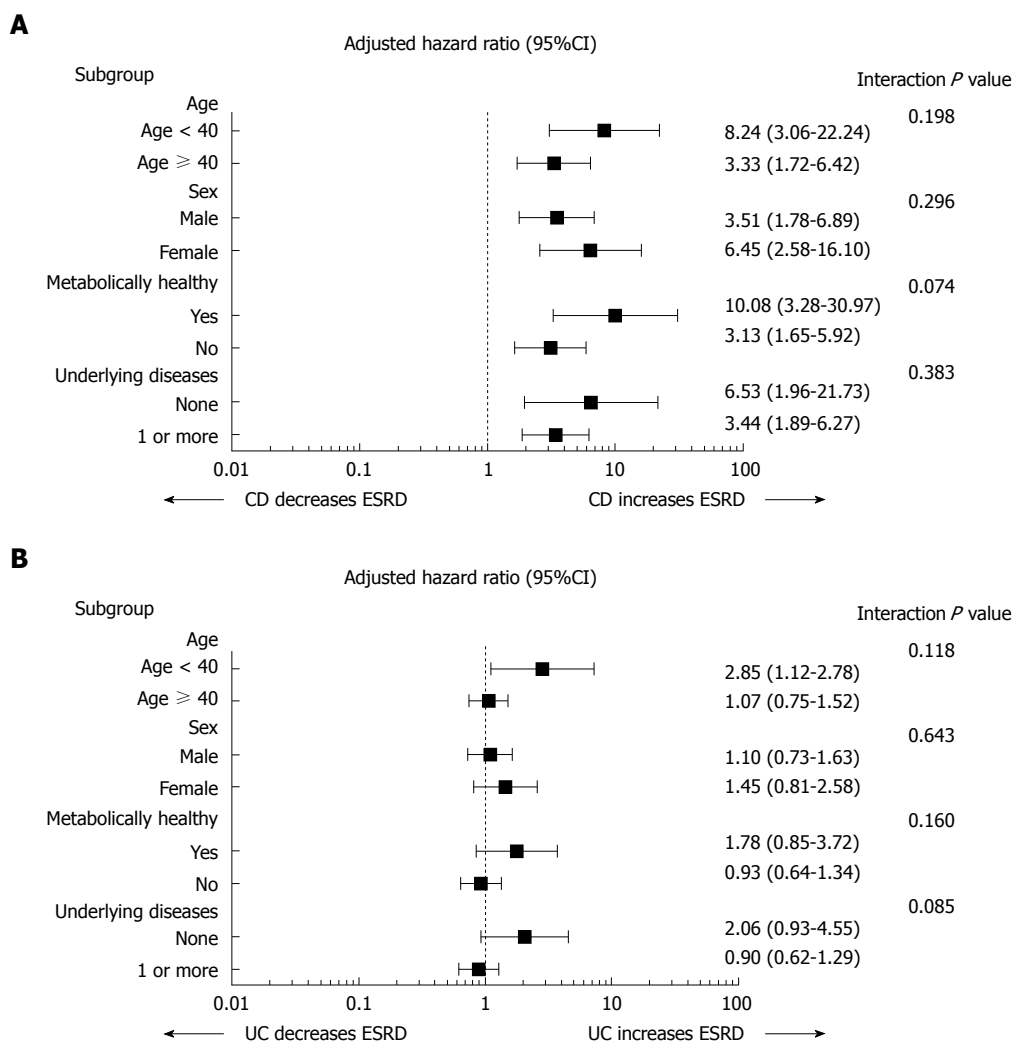


Figure 2 Analysis of end-stage renal disease in subgroups of patients with inflammatory bowel disease. The cohort was divided into patients with (A) Crohn's disease or (B) ulcerative colitis. Subgroups included younger/older age, male/female sex, patients that were/were not metabolically healthy (defined as the absence of diabetes mellitus, hypertension, and dyslipidemia), and patients with/without underlying disease (defined as the presence of at least one of the following: diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, or hyperuricemia and gout). CD: Crohn's disease; CI: Confidence interval; ESRD: End-stage renal disease; UC: Ulcerative colitis.

years; crude HR = 1.06; 95%CI: 0.98-1.15; *P* = 0.120; Supplementary Table 2). However, after multivariate adjustments for age, sex, place of residence, income, comorbidities and medication use, IBD cohort showed increased risk of all-cause death compared to controls (adjusted HR = 2.15; 95%CI: 1.84-2.51; *P* < 0.001; Supplementary Table 2). The overall mortality rate (per 1000 person-years) was 4.31 in patients with CD, 2.10 in controls (adjusted HR = 2.79; 95%CI: 2.14-3.64; *P* < 0.001; Supplementary Table 3), 4.98 in patients with UC and 5.63 in controls (adjusted HR = 1.98; 95%CI: 1.62-2.41; *P* < 0.001; Supplementary Table 3), respectively.

DISCUSSION

In this nationwide population-based study, we demonstrated that the ESRD incidence was significantly higher in patients with IBD than in controls. The overall incidence of ESRD was 0.49 per 1000 person-years in

the IBD incidence group, during a mean follow-up of 4.9 years. This population-based study was the first to determine the overall incidence and risks of ESRD in patients with IBD.

To date, only a few epidemiological studies had investigated the risk of renal insufficiency in patients with IBD. A retrospective cohort study in Austria showed that renal insufficiency occurred in 11 out of 775 patients with IBD (2.0%). In that study, all patients had CD. Of the 11 patients with renal insufficiency, 2 required regular hemodialysis^[14]. A case-control study in the United States showed that renal insufficiency occurred in 40 of 251 patients with IBD (15.9%). Although more patients with CD experienced renal insufficiency compared to patients with UC, the incidences were not significantly different between groups (18.0% vs 12.0%)^[15]. Our retrospective study included a large population, which represented all nationwide insurance claims data. We found that the incidence of ESRD in patients with CD was approximately 5 times greater than that of controls, but the ESRD

incidence in patients with UC was similar to that of controls. These findings were consistent with findings in previous studies. Although rare, the clinically relevant end-stage events derived from renal insufficiency were significantly different between patients with CD and controls. Therefore, patients with CD should be aware of the potential risk of ESRD.

Several mechanisms might explain why patients with CD have a high risk of ESRD. First, ESRD may result from a systemic inflammatory response via an immunologic mechanism that determines the disease activity of the intestines. Low-grade systemic inflammation was found to contribute to renal dysfunction, and consequently, it has emerged as a novel risk factor for ESRD^[20,21]. Indeed, previous reports have demonstrated that elevated inflammatory and pro-inflammatory cytokines functioned as early predictors of renal insufficiency^[22]. Moreover, serum C-reactive protein (CRP) levels were elevated in patients with ESRD that initiated dialysis^[23]. A clear increase in the serum CRP level was also observed in patients with CD, but not in patients with UC^[24-26]. In addition, serum Interleukin 6 levels, a key mediator of the synthesis of acute-phase proteins in the liver, was significantly elevated in patients with CD compared to those with UC and healthy controls^[25,27]. Patients with CD exhibit extensive transmural inflammation and patients with UC exhibit inflammation that is typically localized to the mucosa. Consequently, it can be hypothesized that a systemic inflammatory process, derived from the inflamed intestine, might become more severe in CD than in UC; in turn, this systemic inflammation might exacerbate renal function impairments, which might eventually lead to ESRD. This hypothesis is consistent with results from previous study on the epidemiology of EIMs in patients with IBD^[28,29]. This study reported that the prevalence of EIMs was higher among patients with CD than among those with UC. Another potential mechanism for the development of ESRD in patients with CD might be related to autoimmune susceptibility, which is involved in the pathogenesis of CD. Finally, ESRD might be induced by the secondary complications of chronic intestinal inflammation, such as metabolic or nutritional disorders^[12,13]. Especially in CD, nutritional problems, such as dehydration and electrolyte depletion, are more prominent due to persistent inflammation of the intestine and repeated intestinal resection, leading to electrolyte abnormalities and recurrent acute renal failure, resulting in CKD^[30].

Of the renal manifestations of IBD, the following manifestations are more common in patients with CD. First, nephrolithiasis may occur in association with fat malabsorption and excessive absorption of oxalate in the intestine of the CD. The prevalence of recurrent nephrolithiasis in patients with CD is up to five times higher than the general population, which may be the cause of the ESRD^[31,32]. Also, secondary AA amyloidosis, one of the rare complications of IBD, can occur in about 0.3% to 10.9% of patients with CD, from 0% to

0.7% of patients with UC, and can cause proteinuria, nephrotic syndrome and eventually ESRD^[33-37]. Third, asymptomatic urinary abnormalities referring to proteinuria and hematuria were more common in patients with CD than in patients with UC, and these symptoms may be manifestations of glomerular disease, such as glomerulonephritis, which can cause ESRD^[38]. Last, several epidemiologic studies have shown that patients with IBD have an increased risk of developing nonalcoholic fatty liver disease (NAFLD), and up to 33.6% of patients with IBD have NAFLD^[39,40]. NAFLD is also associated with proteinuria and may present poor renal outcome^[41,42]. Therefore, NAFLD may be regarded as a differential diagnosis of asymptomatic urinary abnormalities in IBD and careful consideration should be given to the occurrence of renal insufficiency.

Recently, growing evidence has suggested that IgA nephropathy is closely related to CD^[43]. Ambrez *et al*^[44] showed that IgA nephropathy [24% (20 of 83)], followed by interstitial nephritis [19% (16 of 83)] was the most common diagnosis in patients with IBD who underwent renal biopsy. The prevalence of IgA nephropathy was also significantly higher in patients with IBD than in the general population^[44]. In addition, rapidly progressive IgA nephropathy has been reported in a patient with exacerbation of CD^[45], suggesting a common pathophysiological relationship between IgA nephropathy and CD. The association between IgA nephropathy and CD might be explained by a direct link between the kidneys and the intestine, referred to as the kidney-gut axis. Intestinal tissues from patients with IgA nephropathy and patients with CD showed increased permeability^[46,47]. The destruction of the intestinal epithelial barrier causes an increase in pro-inflammatory cytokines and toxins associated with the intestinal microbiota. These conditions facilitate the translocation of endotoxin and microorganisms from the intestine into the bloodstream, which can lead to a systemic inflammatory reaction and uremic toxicity^[48]. IgA nephropathy is caused by the accumulation of immune complexes that react to food and microbial antigens. In patients with CD, serum IgG and IgA levels were elevated by a mucosal inflammatory response to *Klebsiella pneumoniae* antigen^[49,50]. In addition, a genetic predisposition to CD may be related to genes involved in IgA nephropathy, such as human leukocyte antigen-DR1^[51,52]. Indeed, IgA nephropathy is one of the most common causes of glomerulonephritis, which leads to ESRD in some patients. Consequently, the fact that the pathogenesis of CD and IgA nephropathy are closely related might explain why patients with CD have a high risk of ESRD. However, in the present study, we did not evaluate the proportion of patients with CD that developed ESRD through IgA-related nephropathy.

In general, we found that patients with CD were at significantly higher risk of developing ESRD than patients with UC and controls, regardless of age, sex, comorbidities. However, among patients with CD, the

risk of ESRD was more prominent in patients that were younger, were metabolically healthy, and were not diagnosed with DM, hypertension, or dyslipidemia. In contrast, among patients with UC, only a younger age was significantly associated with the risk of developing ESRD. These findings suggested that individuals that are generally at low risk of ESRD (*i.e.*, young, healthy individuals) might acquire a relatively high risk of developing ESRD after they develop IBD. Considering that CD onset peaks at a young age and that IBD diseases have a lifelong course, all patients with IBD, even younger patients without any metabolic risk of ESRD, should be monitored regularly for signs of renal insufficiency.

In previous studies, it is still controversial whether IBD increases mortality^[53-55]. However, after adjusting for age, sex, place of residence, income, comorbidities and medication use, we demonstrated that overall mortality was 2.79-fold higher in the CD cohort and 1.98-fold higher in the UC cohort compared to the control groups. This suggests that IBD itself may be an independent risk factor for death. In our study, the overall mortality incidence in patients with UC was significantly lower than the control group, suggesting that the low incidence of ESRD in patients with UC was not due to premature death of patients with UC before turning to ESRD or poor candidates of dialysis. However, data on the cause of death could not be obtained from our study, so further study should be conducted on the cause-specific mortality of IBD.

This study had some limitations, primarily due to the retrospective study design from the claims data. First, because the severity of IBD and ESRD was not available from the NHI database, we could not determine the associations between severity of IBD, risk of developing ESRD, and the severity of ESRD in this study population. Second, 5-ASA was clearly associated with chronic interstitial nephritis in case reports although a previous review indicated that 5-ASA treatments did not increase the risk of developing renal impairment in patients with IBD^[56-59]. In this study, however, patients that were treated with 5-ASA within 1 year of the CD diagnosis showed a lower risk of developing ESRD than those treated without 5-ASA. The 5-ASA therapy might not have a protective effect on the development of ESRD, but serve as a confounder that represents relatively mild-to-moderate activity of CD. Future prospective studies are required to determine whether 5-ASA might contribute to ESRD development in patients with IBD.

In conclusion, the risk of ESRD was elevated in CD, but not in UC. Therefore, patients with CD should be monitored carefully for signs of renal insufficiency.

ARTICLE HIGHLIGHTS

Research background

Patients with inflammatory bowel disease (IBD) may develop a variety of extra-intestinal manifestations (EIMs) including renal manifestation. Renal manifestation of IBD itself, dehydration, malnutrition, and metabolic problems can exacerbate renal function and lead to end-stage renal disease (ESRD).

Research motivation

Previous studies have reported the epidemiology of renal insufficiency, but not ESRD because of the rare incidence in patients with IBD.

Research objectives

To estimate the incidence and risk of ESRD in patients with IBD.

Research methods

From January 2010 to December 2013, patients with Crohn's disease (CD) and ulcerative colitis (UC) were identified, based on both the International Classification of Diseases, 10th revision (ICD-10) and the rare, intractable disease registration program codes from the National Health Insurance database in South Korea. We compared 38812 patients with IBD to age- and sex-matched controls without IBD (ratio 1:3). Patients newly diagnosed with ESRD were identified with the ICD-10 code. The Kaplan-Meier method was used to estimate the cumulative probability of ESRD in patients with IBD.

Research results

Incidence of ESRD is significantly higher in patients with IBD compared to age- and sex-matched controls without IBD. The incidence of ESRD in patients with CD was approximately 5 times higher compared to non-IBD controls, but not in those with UC. Patients with CD are at a statistically significant risk of developing ESRD regardless of age, sex, comorbidities.

Research conclusions

The risk of ESRD was elevated in patients with CD, but not UC.

Research perspectives

Careful monitoring for signs of renal insufficiency is recommended for the patients with IBD, especially CD. Based on our findings, further investigations are needed to determine the best strategies for prevention of renal insufficiency in patients with CD.

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