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Increased Risk of End-stage Renal Disease in Patients with Inflammatory Bowel Disease : A Nationwide Population-based Study

염증성 장질환 환자에서 말기 신부전의 위험도 분석

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Abstract

Increased Risk of End-stage Renal Disease in Patients with Inflammatory Bowel Disease : A Nationwide Population-based Study

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Background/Aim: The association between end-stage renal disease (ESRD) and inflammatory bowel disease (IBD) remains unclear. We investigated the risk of ESRD among patients with IBD using a nationwide population-based claim data.

Methods: We conducted a retrospective cohort study using data from the National

Health Insurance (NHI), a mandatory health insurance program covering about 97% of the Korean population. From 2010 to 2013, patients with Crohn's disease (CD) and Ulcerative colitis (UC) who were registered in the NHI data were identified through both ICD-10 codes (K50 and K51) and the rare/intractable disease registration program codes which provide co-payment reduction of up to 90% in Korea. We compared 38,812 IBD patients with non-IBD age and sex-matched individuals with a ratio of 1:3. Patients who were newly diagnosed with ESRD were identified through ICD-10 code. The Kaplan–Meier method was used to estimate the cumulative probability of ESRD in patients with IBD.

Results: The study participants with IBD comprised 23,680 male (61.0%), and the mean age was 40.0 years. IBD was significantly associated with high income, urban residence, high prevalence of congestive heart failure, ischemic heart disease, hyperuricemia and gout, and low prevalence of diabetes, hypertension, dyslipidemia. During a mean follow-up of 4.9 years, ESRD was newly detected in 79 (0.2%) of the IBD group and 166 (0.1%) of the controls, respectively. The incidence rate of ESRD in patients with IBD was 0.42 per 1,000 person-years. The adjusted risk of ESRD in patients with IBD was significantly higher compared to control group (adjusted hazard ratio [HR], 1.67; 95% confidence interval [CI] , 1.27–2.18; $p<0.001$). Among patients with CD, incidence rate (per 1,000 person-years) of ESRD was 0.51, compared to 0.13 in controls (adjusted HR, 3.98; 95% CI, 2.31-6.85; $p<0.001$). However, there was no significant difference in incidence rate of ESRD between UC and control groups (0.37 vs. 0.37 per 1,000 person-years;

adjusted HR, 1.22; 95% CI, 0.88-1.70; p=0.307). The impact of CD on ESRD significantly increased in patients without any metabolic disease including diabetes, hypertension and dyslipidemia (adjusted HR, 10.08; 95% CI, 3.28-30.97), compared to those with metabolic diseases (adjusted HR, 3.13; 95% CI, 1.65-5.92; p=0.074 by interaction analysis).

Conclusion: The risk of ESRD increased in patients with CD, but not UC. Patients with CD should be monitored carefully for the development of renal insufficiency, especially in those without metabolic syndrome.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; End stage renal disease; Epidemiology

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Introduction

End stage renal disease (ESRD) has been emerged as a one of the most important public health issues in the world. ESRD increases the risk of premature death and lowers quality of life [1-3]. In addition, the prevalence of ESRD is expected to rise over the next several decades due to the population aging, increased prevalence of diseases such as type 2 diabetes mellitus (DM) and hypertension. And the renal replacement therapy, either dialysis or renal transplantation, cause enormous socio-economic costs.[4] Therefore, early identification and prevention of risk factors for ESRD seems to be important for reducing these burdens.

Age, diabetes mellitus, hypertension, obesity, smoking, history of cardiovascular disease, hyperlipidemia and hyperuricemia have been identified for decades as a traditional independent risk factors for ESRD[5, 6]. By identifying new risk factors that are independent of these traditional risk factors, we will be able to stratify risk groups and implement more intensive prevention strategies for the groups. Recently, several studies have reported that low grade systemic inflammation contributes to renal dysfunction and has emerged as a novel risk factor for ESRD.[7-9] Inflammatory and pro-inflammatory markers were elevated in mild renal disease and acted as predictors of renal function[10] and median level of C-reactive protein(CRP) was also elevated in patients with ESRD who initiated dialysis[11]. Although the mechanism has not yet been clearly elucidated, vascular

damage due to oxidative stress and endothelial dysfunction are likely to act. Assessing the association between ESRD and diseases that cause chronic inflammation is essential because it can confirm the contribution of inflammation to ESRD.

Inflammatory bowel disease (IBD), which is divided into Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease mainly involving the intestines. The incidence of IBD in Asia is still lower than in the West, but the incidence and prevalence of IBD are increasing worldwide and the burden is also rising[12, 13]. In addition to the intestinal manifestation, various extra-intestinal manifestations (EIM), including renal involvement, can occur and are important because they can lead to high severity and life-threatening consequences by itself. Renal EIM may result in impaired renal function. Kidney damage can occur not only by the disease itself, but also by secondary extra intestinal complication (malnutrition) or side effect of treatment (5-aminosalicylates or cyclosporine)[14, 15]. But there are scanty data about frequency of renal insufficiency in IBD patients[16, 17], and there is no study about the incidence of ESRD in IBD patients and the association of ESRD and IBD. So, we aimed to assess the incident ESRD in IBD patients and the relationship between ESRD and IBD using nation-wide population based long-term follow-up data.

Materials & Methods

Data source

We conducted a retrospective cohort study using the National Health Insurance (NHI) database. The Korean government provides the NHI, a mandatory health insurance program covering about 97% of the Korean population (Approximately 50 million). Data from the NHI database includes demographic information, medical treatment, outpatient and inpatient care, disease diagnosis, prescription, procedure records. NHI data represents individuals with non-identifiable codes to protect personal information.[18] In 2006, the NHI established a registration program for rare intractable diseases (RID), including IBD and ESRD, so that those enrolled in the program could be provided with enhanced reimbursement for medical costs associated with these diseases. To qualify for enrollment in this special co-payment program, patients must meet the diagnostic criteria provided by the NHI and be approved by a physician. Therefore, the RID database provides reliable and proven data. In this context, the diagnostic codes were defined by International Classification of Diseases, tenth revision (ICD-10) code and special code (V code) registered in RID database [19].

Patient Identification

Among IBD patients enrolled with both V code and ICD-10 code in NHI data from 2010 to 2013, patients without a history of ESRD during the washout period from 2002 to 2009 were extracted as IBD cohort. In order to identify patients with IBD, CD patients were defined as using both ICD-10 code K50 and V code V130, and UC patients were defined as using both ICD-code K51 and V code V131. IBD patients must meet the diagnostic criteria of clinical features, endoscopic findings, and histologic findings to be enrolled in the RID program and to be defined as V code. The accuracy of these diagnostic criteria has already been confirmed in previous published studies. [19, 20] We defined a newly enrolled IBD patient group from 2010 to 2013 as an "incident group", and defined a group of patients who were formerly coded as IBD and reimbursed for IBD during 2010 to 2013 as a “prevalent group”. In order to select non-IBD control cohort, individuals who were not diagnosed with IBD and ESRD in 2010 were randomly selected at a 3:1 ratio for controls to cases as age- and sex- matched controls (n=116,436). Randomization was performed using the SAS algorithm. The data for these cohorts were included until 2015. Since personal information about this cohort is encrypted and all data are anonymous, informed consent was not obtained. This study protocol was approved by the Seoul National University Hospital Institutional Review Board (H-1703-107-840).

Definitions

The primary end point of this study was the newly developed ESRD during the follow up period. ESRD was defined using the combination of ICD-10 code (N18-19, Z49, Z94.0, Z99.2) and V codes registered for chronic renal failure patients undergoing hemodialysis (V001), peritoneal dialysis (V003), or kidney transplantation (V005) as defined in the previous study[21]. Because all patients undergoing dialysis or kidney transplantation are enrolled in the RID program, we were able to identify and analyze data of all ESRD patients in the South Korean population. Patients without ESRD during follow up were censored on the last day of follow up or on the day of death. In this study, hypertension (I10-13, I15 & medication), DM (E11-14), dyslipidemia (E78& medication), congestive heart failure (I50), ischemic heart disease (I20-I25), hyperuricemia and gout (E79, M10) were defined as baseline comorbidities using ICD-10 code. The validity of the definitions for these comorbidities and covariates has already been demonstrated in previous studies.[22, 23]

Statistical analysis

Data for continuous variables are presented as mean with standard deviations, and data for categorical variables are presented as numbers with percentages. The differences between the cohorts were analyzed using independent *t*-tests and χ^2

tests according to baseline characteristics and comorbidities. The incidence rates (IR) of ESRD were calculated by dividing the number of events by 1,000 person-years of follow-up for each group. To identify the risk of new- onset ESRD associated with IBD, the hazard ratio (HR) and 95% confidence interval (CI) of the ESRD adjusted for baseline characteristics and covariates using cox proportional hazard regression models were estimated. The cumulative incidence of ESRD among each group was compared using the Kaplan-Meier method with the log-rank test. Statistical analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA) for Windows. A *P* value <0.05 was considered statistically significant.

Results

From 2010 to 2015, a total of 38,812 IBD patients were enrolled as IBD cohort and were followed for an average of 4.9 years. The mean age of the IBD cohort was 40.0 ±16.7 years and 61.0% were male. In IBD cohort, there were 12,585 patients with CD and 26,227 patients with UC. Age, sex matched 116,436 subjects were enrolled in a non-IBD cohort and were followed for an average of 4.9 years. The baseline demographic and clinical characteristics of both groups are summarized in Table 1.

The residence area and income distribution of the IBD cohort were different from that of the non IBD cohort. Compared with the non-IBD cohort, patients with IBD had lower prevalence of DM(4.2% vs 5.0%; $p<0.001$), hypertension(11.6% vs 12.9%; $p<0.001$), dyslipidemia(7% vs 7.4%; $p=0.009$), and more likely to have congestive heart failure(0.9% vs 0.7%; $p<0.001$), ischemic heart disease(4.5% vs 3.5%; $p<0.001$), hyperuricemia and gout(1.7% vs 1.3%; $p<0.001$), all of which were adjusted when assessing the risk of ESRD. The same trend was observed when IBD patients were classified as CD and UC (Table 1).

During the follow-up period, ESRD was diagnosed in 79(0.2%) of the IBD cohort and in 166(0.1%) of the non-IBD cohort. Overall, the incidence rate for ESRD was 43% higher in IBD cohort than non-IBD cohort (0.42 vs 0.29 per 1,000 person-

years, crude HR = 1.43, 95% CI = 1.09-1.87, p=0.009) (Table 2). The Kaplan-Meier analysis showed that the cumulative incidence of ESRD was significantly higher in the IBD cohort than in the non-IBD cohort (log-rank test, P=0.009) (Figure 1A). After multivariate adjustments for age, sex, residence, income, and associated comorbidities such as DM, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, hyperuricemia and gout, the risk of ESRD development was 67% higher (95% CI = 1.27-2.18, p<0.001) in the IBD cohort than in the non-IBD cohort. Even when the IBD patients were divided into incident group and prevalent group respectively, the risk of ESRD after multivariate adjustment was 72% higher (95% CI = 1.17-2.52) in the incident group and 63% higher (95% CI = 1.18-2.27) in the prevalent group than in the non-IBD cohort respectively (p<0.001) (Table 2). Table 3 shows the risk of ESRD in two types of IBD, UC and CD. After multivariate adjustment, the risk of ESRD in CD patients was significantly higher (adjusted HR= 3.98, 95% CI = 2.31-6.85, p<0.001) than in non-CD patients, but not in UC patients (adjusted HR= 1.22, 95% CI = 0.88-1.70, p=0.307). When both groups were classified as incident and prevalent groups, the risk of ESRD was significantly higher in incident CD group (adjusted HR= 4.21, 95% CI = 2.12-8.35) and prevalent CD group (adjusted HR= 3.81, 95% CI = 2.03-7.16) than non-CD patients (p<0.001), but not in incident UC group (adjusted HR= 1.19, 95% CI = 0.73-1.96) and prevalent UC group (adjusted HR= 1.24, 95% CI = 0.83-1.84) (p=0.814). The Kaplan-Meier analysis showed that the cumulative incidence of ESRD in patients with CD was significantly higher than in non CD

control (log-rank test, *P*=<.001), but not in patients with UC(log-rank test, *P*=0.942). (Figure 1B,1C)

In the subgroup analysis, the effects of CD and UC on the development of ESRD were evaluated (Figure 2). CD increased the risk of ESRD, especially in patients without metabolic comorbidities (HTN, DM, and dyslipidemia). The HR of all subgroups of CD was greater than 1, indicating that the CD consistently elevated the risk of ESRD. However, UC did not significantly increase the risk of ESRD in the subgroup analysis.

Table1. Baseline characteristics

No. (%)	IBD			CD			UC		
	Non-IBD cohort (n=116436)	IBD cohort (n=38812)	*P* value	Non-CD group (n=37755)	CD group (n=12585)	*P* value	Non-UC group (n=78681)	UC group (n=26227)	*P* value
AGE, years	40.0±16.7*	40.0±16.7*	1	30.7±14.6*	30.7±14.6*	1	44.4±15.8*	44.4±15.8*	1
<15	3639(3.1)	1213(3.1)	1	2562(6.8)	854(6.8)	1	1077(1.4)	359(1.4)	1
15-29	33,138(28.5)	11,046(28.5)		18834(49.9)	6278(49.9)		14304(18.2)	4768(18.2)	
30-44	34,800(29.9)	11,600(29.9)		10215(27.1)	3405(27.1)		24585(31.3)	8195(31.3)	
≥45	44,859(38.5)	14953(38.5)		6144(16.3)	2048(16.3)		38715(49.2)	12905(49.2)	
Male gender	71,040(61.0)	23680(61.0)	1	26451(70.1)	8817(70.1)	1	44589(56.7)	14863(56.7)	1
Rural area	62,045(53.3)	19312(49.8)	<.001	20043(53.1)	6163(49.0)	<.001	42002(53.4)	13149(50.1)	<.001
Lowest income 20%	33,008(28.4)	9316(24)	<.001	10705(28.4)	3229(25.7)	<.001	22303(28.6)	6087(23.2)	<.001
Diabetes mellitus	5,786(5.0)	1612(4.2)	<.001	845(2.3)	280(2.2)	0.931	4941(6.3)	1332(5.1)	<.001
Hypertension	14,958(12.9)	4494(11.6)	<.001	2294(6.1)	665(5.3)	0.001	12664(16.1)	3829(14.6)	<.001
Dyslipidemia	8,620(7.4)	2718(7)	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)	<.001	119(0.3)	85(0.7)	<.001	662(0.8)	271(1.0)	0.004

Ischemic heart disease	4,028(3.5)	1747(4.5)	<.001	616(1.6)	381(3.0)	<.001	3412(4.3)	1366(5.2)	<.001
Gout, hyperuricemia	1,552(1.3)	650(1.7)	<.001	320(0.9)	211(1.7)	<.001	1232(1.6)	439(1.7)	<.001
Follow-up period, years	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

IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis. * Mean±SD.

Table 2. Incidence and risk of ESRD in IBD patients compared with non-IBD controls.

	Total number(n)	ESRD cases (n)	Person-years	ESRD incidence (per 1000 person-years)	Crude HR (95% CI)	*p* value	Model 1[a] HR (95% CI)	*p* value	Model 2[b] HR (95% CI)	*p* value
Total IBD						0.009		0.009		<0.001
Non-IBD cohort	116,436	166	568,575	0.29	1(reference)		1(reference)		1(reference)	
Total IBD cohort	38,812	79	189,245	0.42	1.43(1.09-1.87)		1.43(1.09-1.87)		1.67(1.27-2.18)	
IBD group						0.013		0.004		<0.001
Non-IBD cohort	116,436	166	568,575	0.29	1(reference)		1(reference)		1(reference)	
Incident IBD group	16,606	32	65,646	0.49	1.71(1.17-2.50)		1.89(1.29-2.73)		1.72(1.17-2.52)	
Prevalent IBD group	22,206	47	123,600	0.38	1.29(0.93-1.78)		1.23(0.89-1.70)		1.63(1.18-2.27)	

ESRD, End stage renal disease; IBD, Inflammatory bowel disease; HR, Hazard ratio; CI, Confidence interval.

[a] Model 1 : adjusted for age and sex.

[b] Model 2 : adjusted for model 1 + region, income, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, gout and hyperuricemia

Table 3. Incidence and risk of ESRD in CD and UC patients compared with controls

	Total number(n)	ESRD cases (n)	Person-years	ESRD incidence (per 1000 person-years)	Crude HR (95% CI)	*p* value	Model 1[a] HR (95% CI)	*p* value	Model 2[b] HR (95% CI)	*p* value
Total CD						<.001		<.001		<.001
Non-CD patients	37,755	24	184,988	0.13	1(reference)		1(reference)		1(reference)	
Total CD patients	12,585	31	61,189	0.51	3.90(2.29-6.65)		4.00(2.35-6.82)		3.98(2.31-6.85)	
CD group						<.001		<.001		<.001
Non-CD patients	37755	24	184,988	0.13	1(reference)		1(reference)		1(reference)	
Incident CD group	5586	14	21,836	0.64	4.92(2.53-9.57)		5.18(2.66-10.07)		4.21(2.12-8.35)	
Prevalent CD group	6999	17	39,353	0.43	3.34(1.79-6.23)		3.37(1.81-6.29)		3.81(2.03-7.16)	
Total UC						0.941		0.961		0.307
Non-UC patients	78681	142	383,587	0.37	1(reference)		1(reference)		1(reference)	
Total UC patients	26227	48	128,056	0.37	1.01(0.73-1.40)		1.01(0.73-1.40)		1.22(0.88-1.70)	
UC group						0.821		0.821		0.814
Non-UC patients	78681	142	383,587	0.37	1(reference)		1(reference)		1(reference)	
Incident UC group	11020	18	43,810	0.41	1.14(0.70-1.87)		1.27(0.77-2.08)		1.19(0.73-1.96)	

Prevalent UC group	15207	30	84,247	0.36	0.95(0.64-1.41)	0.90(0.61-1.33)	1.24(0.83-1.84)

ESRD, End stage renal disease; CD, Crohn's disease; UC, Ulcerative colitis; CI, HR, Hazard ratio; Confidence interval.

[a] Model 1 : adjusted for age and sex.

[b] Model 2 : adjusted for model 1 + region, income, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, gout and hyperuricemia

Figure 1. Cumulative incidence of End stage renal disease according to the presence of Inflammatory bowel disease (A), Crohn's disease (B) and Ulcerative colitis(C).

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = Ulcerative colitis.

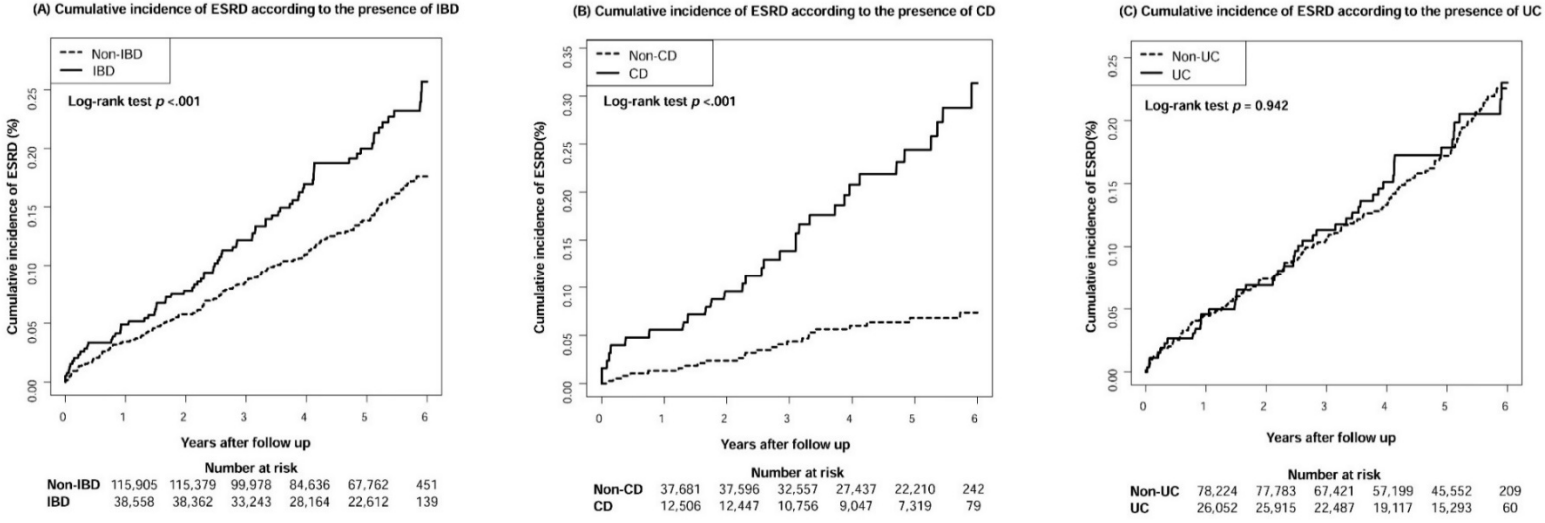
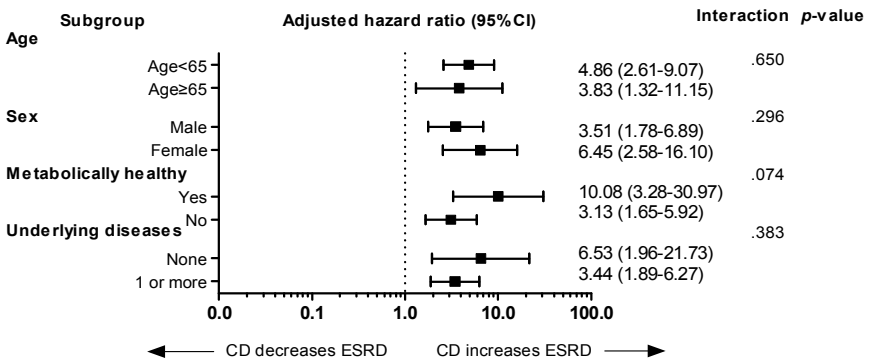
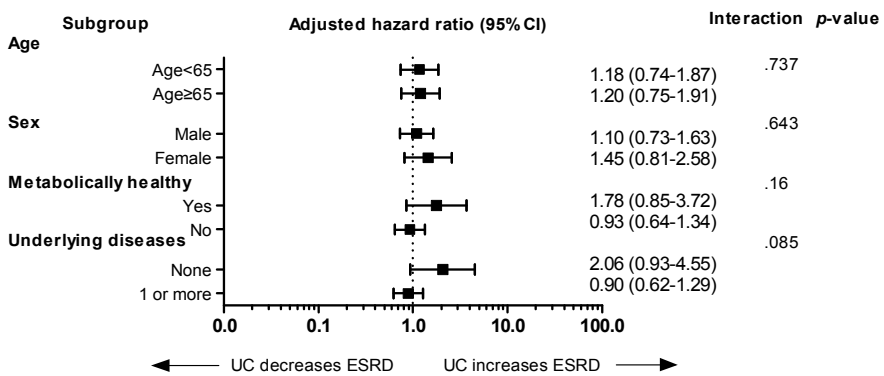


Figure 2. Subgroup analysis of the impact of Crohn's disease (A) and Ulcerative colitis (B) on development of End stage renal disease.

CD = Crohn's disease; UC = Ulcerative colitis; ESRD= End stage renal disease; CI = Confidence interval



(A) Crohn's disease



(B) Ulcerative colitis

Discussion

ESRD is one of the most important public health problems in the world, so it is important to identify its risk factors [1-3]. Previous studies on the association of ESRD with chronic inflammatory disease [24-28] have suggested that systemic inflammation is one of the mechanisms by which ESRD is induced. In this study, we found that patients with IBD, one of the chronic inflammatory diseases, had a significantly higher risk of ESRD than the general population. In this nationwide retrospective cohort study using NHI data, the risk of development of ESRD in IBD cohort was 67% higher than in the non-IBD cohort when adjusted for age, sex, residence, income level, and accompanying disease.

Previously, only a few studies reported the incidence of renal insufficiency in IBD patients, each of which was a retrospective study in one tertiary care center[16, 17]. Christian Primas showed that renal insufficiency occurred in 11 out of 775 IBD patients (2.0%) during the period from March 2006 to December 2007, all of whom were patients with CD and did not occur in patients with UC, and there was a statistically significant difference(p=0.04). Of these, 2 patients with renal insufficiency required regular hemodialysis[17]. Brian Lewis reported that renal insufficiency occurred in 40 of 251 patients with IBD (15.9%) from 2009 to 2010 and there was no statistically significant difference in the frequency of renal insufficiency between the CD and UC patients (18.0% vs 12.0%; p=0.20)[16].

However, to date, there have been no studies showing the incidence of ESRD in IBD patients, and our study is the first to show this.

There are several mechanisms that can explain the higher risk of ESRD in IBD patients than non IBD patients. In 4-23% of IBD patients, renal complications such as nephrolithiasis, glomerulonephritis, tubulointerstitial nephritis, and secondary amyloidosis may occur, all of which may cause renal dysfunction. It may be caused by a systemic inflammatory response, an immunologic mechanism that determines inflammatory disease of the intestine that is directly related to the disease activity of the intestine, or by autoimmune susceptibility independent of the intestinal manifestations, and also be caused by secondary complications of IBD, such as metabolic and nutritional problems [29, 30]. There are several studies showing that drugs such as 5-aminosalicylates affect renal function, but it is still controversial whether the deterioration of renal function is due to the EIM of IBD or the side effect of the drug [31-33]. Ambrez et al. reported that the prevalence of IgA nephropathy was significantly higher in IBD patients than in non-IBD patients [34]. It can be explained by complex interactions such as mucosal inflammation and loss of antigenic exclusion, and tolerance, chronic immune stimulation, and dysregulated IgA production[35].

Also, some recent studies have emphasized the close link between kidney and GIT, which is recently referred to as the kidney-gut axis. When the intestinal epithelial barrier is destroyed and the pro-inflammatory molecules and toxins associated with the intestinal microbiota increase, intestinal translocation of endotoxin and live bacteria into the bloodstream from the gut may occur, leading to

a systemic inflammatory reaction and uremic toxicity in patients with chronic kidney disease [36, 37]. Although these complex immune mechanism interactions and gut microbiota may cause renal insufficiency in IBD patients, prospective long-term follow-up with renal biopsy data will be needed to clarify the impact of IBD on ESRD.

In this study, when IBD patients were classified as CD and UC patients, the risk of ESRD was 3.98 times higher in patients with CD than general population, but not significantly different between patients with UC and the general population after multivariate adjustment. Since inflammation is usually transmural in CD but typically localized to the mucosa in UC[38], it can be hypothesized that systemic inflammation associated with mucosal immune response may cause more severe inflammation in CD than UC, which may exacerbate renal function and eventually lead to ESRD. Previously published studies on EIMs of IBD [39-41] have shown that the frequency of EIMs is generally higher in CD than in UC, suggesting the above hypothesis, but the renal EIM of IBD is very rare and there is no data to compare the incidence of renal EIM in CD and UC until now. In subgroup analysis, CD generally increased the risk of ESRD, especially in metabolically healthy patients without any of the comorbidities including hypertension, DM, and dyslipidemia. The reason for the higher risk of ESRD in these patients is still unclear and needs further investigation, but it is certain that CD itself can cause renal insufficiency and may act as a potential risk for ESRD and screening for renal function should be more intensive in patients with CD without comorbidities known as a potential risk for ESRD.

There are several strengths of our research. First, it was the initial study to confirm the impact of IBD on ESRD. Second, the large sample size using NIH data, including nearly all Korean population and the RID registry program, a diagnostic criteria used to define ESRD and IBD, made the diagnosis of ESRD and IBD more rigorous. Therefore, the results of the analysis became more reliable. Third, when IBD patients were divided into incident group and prevalent group, similar results were obtained as in all IBD patients, demonstrating the validity of the study. Finally, this study suggests that IBD is an independent risk factor for ESRD because almost all comorbidities that can act as a risk factor for ESRD has been taken into account and adjusted.

There are, however, severe limitations in this study. First, since we could not assess the severity of IBD, we did not know if the progression of IBD would increase the risk of ESRD. Second, it is possible that the impact of IBD on ESRD has been underestimated or overestimated. Because IBD, ESRD, and other comorbidities were identified with claim data using diagnostic codes and the information on lifestyle or personal health behaviors that are thought to be associated with ESRD has not been investigated. However, the potential biases were minimized using the NHI data, which included about 97% of the Korean population, and the RID database with strict diagnostic criteria and the refined definition of diseases used in previous studies[22, 23]. Finally, we have identified a statistically significant association between the IBD and ESRD development, but the pathophysiological mechanism requires further study in the future.

In conclusion, our data indicate that the risk of ESRD in patients with CD was

higher than that of the general population, but not in patients with UC. Therefore, our study suggests that screening of renal function and complication is regularly needed in IBD patients, especially in CD patients, and that clinical attention and development of screening programs are needed.

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초 록

연구 배경/ 목적 : 말기 신부전의 발생 위험과 염증성장질환의 연관성은 아직 명확하지 않으며 연구된 바가 없다. 그러므로 우리는 염증성장질환 환자의 말기신부전 발생 위험이 염증성장질환이 없는 사람에서 보다 높은지 확인하기 위하여 전국 규모의 인구기반 연구를 수행하였다.

연구 방법 : 우리는 한국 인구의 97%를 포함하는 국민건강보험공단의 데이터를 이용하여 후향적 코호트 연구를 실시하였다. 2010년부터 2013년까지 국민건강보험공단 데이터베이스에 국제질병사인분류코드(ICD-10 코드 K50과 K51)와 희귀난치성질환 산정특례 코드로 모두 등록된 크론병과 궤양성대장염 환자를 선정하였다. 우리는 38,812 명의 염증성 장질환 환자와 연령 및 성별이 짝지어진 염증성장질환이 없는 사람을 1:3 비율로 선정하여 비교하였다. 말기 신부전으로 새로이 진단받은 환자들은 국제질병사인분류코드를 통해 확인되었다. 카플란-메이어 생존분석 방법은 염증성장질환 환자에서 말기신부전의 누적 확률을 평가하는데 사용되었다.

연구 결과 : 염증성장질환 환자 중 23,680명(61퍼센트)이 남성이었고,

평균 연령은 40.0세였다. 염증성장질환 환자가 대조군에 비해 더 소득수준이 높고, 도시에 거주하는 경향이 있으며 울혈성 심부전, 허혈성 심장질환, 고뇨산혈증과 통풍의 유병률이 더 높았으나 당뇨병, 고혈압, 이상지질혈증의 유병률은 더 낮았다. 4.9년의 평균 추적관찰 기간 동안 말기 신부전은 염증성장질환 환자에서 79명, 대조군에서 166명에서 새로이 진단되었다. 염증성장질환 환자의 말기신부전 발병률은 1,000인년 당 0.42였다. 염증성장질환 환자에서 보정된 말기 신부전의 발생위험은 대조군에 비해 유의하게 높았다(보정된 위험비=1.67, 95퍼센트 신뢰 구간=1.27−2.18, 유의수준 <0.001). 염증성장질환 중 크론병 환자의 말기 신부전의 발병률 (1000인년 당)은 0.51이었고, 대조군에서는 0.13이었다(보정된 위험비=3.98, 95퍼센트 신뢰 구간=2.31−6.85, 유의수준 <0.001). 그러나 궤양성대장염 환자의 말기 신부전 발병률은 대조군과 유의한 차이가 없었다(1,000인년 당 0.37 vs. 0.37; 보정된 위험비 =1.22, 95퍼센트 신뢰 구간=0.88−1.70, 유의수준=0.307). 말기 신부전에 대한 크론병의 영향은 대사성 질환이 있는 사람들 (보정된 위험비 =3.13, 95퍼센트 신뢰 구간=1.65−5.92)에 비해 당뇨병, 고혈압 및 이상 지질혈증을 포함한 어떠한 대사성 질환도 없는 환자에서 유의하게 증가했다(보정된 위험비=10.08, 95퍼센트 신뢰 구간=3.28−30.97, 상호작용 분석시 유의수준=0.074,).

결론 : 이번 전국 인구기반 연구에서 크론병 환자에서의 말기 신부전 발

생위험은 일반인구에 비해 높았지만, 궤양성 대장염 환자에서는 큰 차이를 나타내지 않았다. 크론병 환자, 특히 대사성 질환을 동반하지 않는 환자는 신 기능부전의 발병을 주의 깊게 관찰 해야한다.

주요어 : 염증성 장질환; 크론병; 궤양성 대장염; 말기 신부전; 역학

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