의학 석사 학위논문

Increased Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease: A Nationwide Population-based Study in Korea

염증성 장질환 환자에서의 불안증과 우울증의 위험도 분석: 전국민 기반 코호트 연구

2018년 02월

서울대학교 대학원

의학과 내과학

최 국 환

A thesis of the Master's degree

염증성 장질환 환자에서의 불안증과 우울증의 위험도 분석: 전국민 기반 코호트 연구

Increased Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease: A Nationwide Population-based Study in Korea

February 2018

The Department of Internal Medicine

Seoul National University College of Medicine

Gukhwan Choi

염증성 장질환 환자에서의 불안증과 우울증의 위험도 분석: 전국민 기반 코호트 연구

지도교수 김 주 성

이 논문을 최 국 환 석사학위논문으로 제출함

2017 년 10 월

서울대학교 대학원

의학과 내과학

최 국 환

최 국 환 의 석사학위논문을 인준함

2018 년 01 월

위 원 장 정 현 채 (인)

부위원장 김 주 성 (인)

위 원 고 재 성 (인)

Abstract

Increased Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease

: A Nationwide Population-based Study in Korea

Gukhwan Choi

Department of Internal Medicine

The Graduate School

Seoul National University

Background/Aims: Inflammatory bowel disease (IBD) may be associated with psychological disorders. The aim of this study was to investigate the risk of anxiety and depression in patients with IBD.

Methods: We conducted a retrospective study using claim data from the National Healthcare Insurance service (NHIS) in Korea. The patients with Crohn's disease (CD) and ulcerative colitis (UC) were identified through both ICD-10 codes and the rare/intractable disease registration program

codes which provide co-payment reduction of up to 90% in Korea. We compared 15,569 IBD patients with 46,707 non-IBD controls matched by age and sex with a ratio of 1:3. Cases with newly diagnosed anxiety and depression were identified through ICD-10 codes in the study population, respectively. The Kaplan–Meier method was used to estimate the cumulative probability of anxiety and depression in IBD patients.

Results: During the mean follow-up of 6 years, IBD patients experienced anxiety and depression more frequently than non-IBD controls, respectively (anxiety: 12.2% vs. 8.7%, $p<0.001$; depression: 8.0% vs. 4.7%, $p<0.001$). In patients with CD, incidence rate (per 1,000 person-years) of anxiety was 19.51, compared to 13.26 in controls (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.40-1.89; $p<0.001$), and incidence rate of depression was 12.79, compared to 6.6 in controls (HR, 2.09; 95% CI, 1.73-2.52; $p<0.001$). In patients with UC, incidence rate (per 1,000 person-years) of anxiety was 28.9, compared to 19.87 in controls (HR, 1.60; 95% CI, 1.44-1.77; $p<0.001$), and incidence rate of depression was 16.49, compared to 9.23 per in controls (HR, 2.00; 95% CI, 1.74-2.30; $p<0.001$). The impact of CD on developing depression was more pronounced in male gender (adjusted HR, 1.58; 95% CI, 1.41-1.76) than in female (adjusted HR, 1.21;

95% CI, 1.00-1.47; p=0.025 by interaction analysis).

Conclusion: The risk of anxiety and depression increased in the patients with IBD, respectively. Patients with IBD would be monitored carefully for the development of mood disorders.

Keywords: Anxiety; Crohn's disease; Depression; Inflammatory bowel disease; Ulcerative colitis.

Student number: 2016-21921

CONTENTS

LIST OF TABLES AND FIGURES

Introduction

Inflammatory bowel disease (IBD), which is divided into Crohn's disease (CD) and ulcerative colitis (UC) is a chronic and recurrent inflammatory conditions of the gastrointestinal tract. CD has an annual incidence of 0–20.2 per 100,000 in North America, 0.3–12.7 per 100,000 in Europe and 0.4-5.0 per 100,000 in Asia and the ulcerative colitis is estimated to be 0–19.2 per 100,000 in North America, 0.6–24.3 per 100,000 in Europe, and 0.8-6.0 per 100,000 in Asia (1, 2). Globally, annual incidence of IBD is on the increasing trend and its annual medical cost is about $18,963 for CD, $15,020 for UC patients, respectively (3). In spite of recent advances in the management for IBD, several studies have shown that IBD may be associated with the development of mood disorders such as anxiety and depression (4-9). The risk of anxiety and depression in IBD has been reported at 29-35% during periods of remission and 80% for anxiety and 60% for depression during relapses (10). In addition, a recent study reported that anxiety and depression were associated with increased medical costs in general medical inpatient suggesting that anxiety and depression still causes a large burden on healthcare system (11). In a literature review, risk factors for anxiety and depression in IBD patients were demographic characteristics, disease

activity/severity, treatments and psychosocial factors (10, 12, 13). On the other hand, anxiety and depression were known to cause the development of IBD and negatively affect the quality of life of IBD patients, suggesting that anxiety and depression are closely related to the clinical course of IBD (12, 13). However, the relationships between mood disorders and IBD remain unclear.

The aim of this study was to investigate the risk of anxiety and depression in patients with IBD through nationwide population-based study in Korea.

Material and Methods

Data source

The NHIS (National Healthcare Insurance Service) database was used for this retrospective cohort study. NHIS is the nationwide comprehensive compulsory health care system which covers approximately 96.6% of the over 48.6 million population of South Korea from 2006 (14). Within NHIS, registration program for rare/intractable diseases (RIDs), such as Crohn's disease and ulcerative colitis, was established and patients with IBD have to register in RIDs which provide co-payment reduction of up to 90% in Korea. To be registered in RIDs, patients need to be satisfied with specific diagnostic criteria and physician certified. We used cases registered in RIDs in NHIS, so our data are verified and reliable.

Patient selection

IBD patients were identified from NHIS database from January 1, 2010 to December 31, 2013 who have not been diagnosed anxiety and depression from January 1, 2002 to December 31, 2009 during washout period. To minimize misclassification, IBD patients were defined as the case who both

ICD-10 codes (K50:CD, K51:UC) and RIDs codes (V130:CD, V131:UC) were satisfied. The diagnostic criteria and validation for IBD were mentioned in previous study (15). Patients newly diagnosed as IBD during January 1, 2010 to December 31, 2013 were defined as the 'incident' group, whereas patients previously diagnosed as IBD and also coded during January 1, 2010 to December 31, 2013 were defined as the 'prevalent' group. Patients diagnosed as IBD before January 1, 2010 but not coded during January 1, 2010 to December 31, 2013 were removed from the NHIS database. The comparison controls were randomly selected from NHIS database and were 1:3 matched by age and sex. All patients followed retrospectively until the new onset anxiety (F40-42) or depression (F32-34) developed. ICD-10 codes for anxiety and depression were mentioned in previous study (16).

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) and categorical variables are presented as number and percentage. To compare characteristics between cohorts, Student t test was used for continuous variables and the chi-square test was used for binary and categorical

variables. The cumulative anxiety and depression incidence for each group was plotted with Kaplan-Meier curves and compared using the log-rank test. Cox regression models were used to assess the risks of new-onset anxiety and depression associated with baseline characteristics such as age, sex, residence, income, underlying diseases (DM, hypertension, dyslipidemia) and therapeutic drug use for IBD within 1 year (immunomodulators, steroids, biologics). The potential effect modification by age, sex, income, residence, underlying diseases and therapeutic drug use for IBD within 1 year was evaluated through stratified analysis and interaction testing using a forest plot. All statistical tests were two-tailed and the significance level was set at $p<0.05$. Statistical analyses were performed using SPSS Statistics, Version 21.0 (IMB Corp., Armonk, NY, USA) and SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA) for Windows. The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (SNUH IRB No. H-1703-107-840).

Results

Baseline and clinical characteristics of the study population

During the mean follow-up of 6 years, IBD and controls were 15,569 (25.0%) and 46,707 (75.0%). Table 1 shows the baseline characteristics between IBD and the other healthy controls. The study population comprised 11,409 males (73.28%) in patients with IBD, 5,009 (78.31%) in CD and 6,400 (69.77%) in UC. The mean age were 32 years in patients with IBD, 25.3 in CD and 36.7 in UC. Among them, residence, income, history of DM, therapeutic drug use for IBD within 1 year presented differences between IBD and healthy controls. In the case of residence, income and therapeutic drug use for IBD within 1 year, when IBD was divided into CD and UC, there were differences compared to controls ($p<0.001$, respectively). Incidence of anxiety and depression in IBD was higher than controls (1,904 (12.2%) vs 4,080 (8.7%), 1,244 (8.0%) vs 2,211 (4.7%), $p<0.001$ respectively). When incidence of anxiety and depression were analyzed in the CD and UC, there were also significant differences compared to controls ($p<0.001$, respectively).

Anxiety and depression risk in IBD

After adjusting confounding factors (age, sex, residence, income, underlying diseases), the Cox proportional hazard analysis shows that IBD was more possible to develop anxiety and depression than controls (Table 2, 3). Both development risks of anxiety and depression were higher in IBD than controls in IBD incident group. In patients with CD, incidence rate (per 1,000 person-years) of anxiety was 19.51, compared to 13.26 in controls (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.40-1.89; $p<0.001$), and incidence rate of depression was 12.79, compared to 6.6 in controls (HR, 2.09; 95% CI, 1.73-2.52; $p<0.001$). In patients with UC, incidence rate (per 1,000 person-years) of anxiety was 28.9, compared to 19.87 in controls (HR, 1.60; 95% CI, 1.44-1.77; $p<0.001$), and incidence rate of depression was 16.49, compared to 9.23 per in controls (HR, 2.00; 95% CI, 1.74-2.30; $p<0.001$). In prevalent gruop, the results were similar. Additionally, the Kaplan-Meier plots shows that IBD patients had a significantly higher risk of anxiety and depression than healthy controls (Figure 1, 2). In patients with CD, cumulative incidence rate of anxiety in 1, 3, 6 years were 0.03, 0.069, 0.115 and cumulative incidence rate of depression in 1, 3, 6 years were 0.027,

0.052, 0.08 (log-rank test, p<0.001, respectively). In patients with UC, cumulative incidence rate of anxiety in 1, 3, 6 years were 0.042, 0.099, 0.167 and cumulative incidence rate of depression in 1, 3, 6 years were 0.026, 0.066, 0.108 (log-rank test, p<0.001, respectively).

Subgroup analyses

Subgroup analyses stratified by age, sex, residence, income, the presence or absence of underlying diseases and therapeutic drug use for IBD within 1 year were performed (Figure 3, 4). The HRs for CD and UC were >1 for mostly subgroups, indicating that IBD consistently increased the risk of anxiety and depression. CD increased the risk of anxiety in patients not taking immunomodulators and UC increased the risk of anxiety in patients not taking steroids and without underlying diseases. On the other hand, CD increased the risk of depression in male and UC increased the risk of depression in patients not taking immunomodulators and without hypertension, dyslipidemia and any underlying diseases.

Table 1. Baseline and clinical characteristics of the study population

No. (%)	IBD			CD			UC		
	Controls‡	IBD	P-value	Controls	CD	P-value	Controls	UC	P-value
Events	46,707	15,569		19,188	6,396		27,519	9,173	
Age, years†	32±13.9	32±13.9	1	25.3±10.7	25.3±10.7	1	36.7±13.9	36.7±13.9	1
<15	3,054(6.54)	1,018(6.54)		2,145(11.18)	715(11.18)		909(3.3)	303(3.3)	
15-29	25,323(54.22)	8,441(54.22)		13,611(70.93)	4,537(70.93)		11,712(42.56)	3,904(42.56)	
30-44	17,505(37.48)	5,835(37.48)		3,363(17.53)	1,121(17.53)		14,142(51.39)	4,714(51.39)	
>45	825(1.77)	275(1.77)		69(0.36)	23(0.36)		756(2.75)	252(2.75)	
Male gender	34,227(73.28)	11,409(73.28)	1	15,027(78.31)	5,009(78.31)	1	19,200(69.77)	6,400(69.77)	1
Residence			<0.001			<0.001			<0.001
Urban	21,924(46.94)	8,125(52.19)		9,003(46.92)	3,398(53.13)		12,921(46.95)	4,727(51.53)	
Rural	24,783(53.06)	74,44(47.81)		10,185(53.08)	2,998(46.87)		14,598(53.05)	4,446(48.47)	
Income*			<0.001			<0.001			<0.001
Q2-4	36,284(77.68)	12,678(81.43)		14,846(77.37)	5,123(80.1)		21,438(77.9)	7,555(82.36)	
Q1	10,423(22.32)	2,891(18.57)		4,342(22.63)	1,273(19.9)		6,081(22.1)	1,618(17.64)	
Underlying diseases									
Diabetes mellitus	1,048(2.24)	305(1.96)	0.035	156(0.81)	54(0.84)	0.810	892(3.24)	251(2.74)	0.016
Hypertension	2,660(5.7)	822(5.28)	0.051	429(2.24)	115(1.8)	0.036	2,231(8.11)	707(7.71)	0.222
Dyslipidemia	1,489(3.19)	529(3.4)	0.200	242(1.26)	78(1.22)	0.800	1,247(4.53)	451(4.92)	0.128
Use of therapeutic drugs									
Immunomodulators	105(0.22)	5,194(33.36)	<0.001	34(0.18)	3,865(60.43)	<0.001	71(0.26)	1,329(14.49)	<0.001
Steroids	12,701(27.19)	8,681(55.76)	<0.001	4,895(25.51)	3,689(57.68)	<0.001	7,806(28.37)	4,992(54.42)	<0.001
Biologics	6(0.01)	1,122(7.21)	<0.001	2(0.01)	932(14.57)	<0.001	4(0.01)	190(2.07)	<0.001
Anxiety	4,080(8.74)	1,904(12.23)	<0.001	1,301(6.78)	617(9.65)	<0.001	2,779(10.1)	1,287(14.03)	<0.001
Depression	2,211(4.73)	1,244(7.99)	<0.001	716(3.73)	437(6.83)	<0.001	1,495(5.43)	807(8.8)	<0.001

*Q1: lower 25%, Q2-4: upper 75%.
†Mean ± SD.
‡Controls: Age, Sex matched
IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis

Table 2. Independent risk of anxiety in patients with IBD and healthy controls

	Events (n)	Follow-Up Duration (Person-Years)	Incidence Rate (Per 1000 Person-Years)	Hazard Ratio (95% C.L.)	P-value
CD					
Controls	1,174	88,547.24	13.26	1(Ref.)	
Prevalent	531	28,348.04	18.73	1.43(1.29-1.59)	<0.001
Incident	212	10,864.02	19.51	1.63(1.40-1.89)	<0.001

UC					
Controls	2,469	124,237.69	19.87	1(Ref.)	
Prevalent	1,126	39,605.5	28.43	1.45(1.35-1.56)	<0.001
Incident	424	14,672.47	28.9	1.60(1.44-1.77)	<0.001

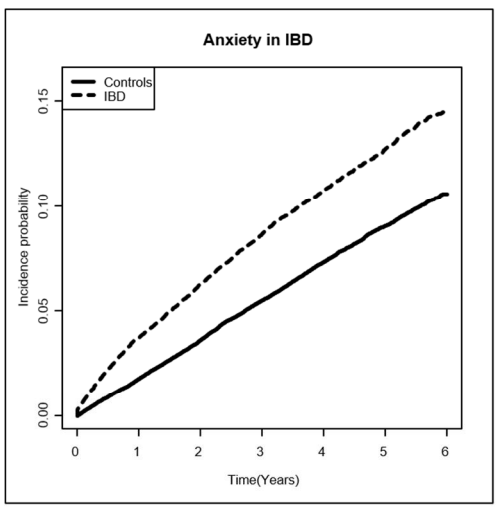
IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis

Table 3. Independent risk of depression in patients with IBD and healthy controls

	Events (n)	Follow-Up Duration (Person-Years)	Incidence Rate (Per 1000 Person-Years)	Hazard Ratio (95% C.L.)	P-value
CD					
Controls	584	88547.24	6.6	1(Ref.)	
Prevalent	352	28348.04	12.42	1.90(1.66-2.16)	<0.001
Incident	139	10864.02	12.79	2.09(1.73-2.52)	<0.001
UC					
Controls	1147	124237.69	9.23	1(Ref.)	
Prevalent	602	39605.5	15.2	1.68(1.52-1.86)	<0.001
Incident	242	14672.47	16.49	2.00(1.74-2.30)	<0.001

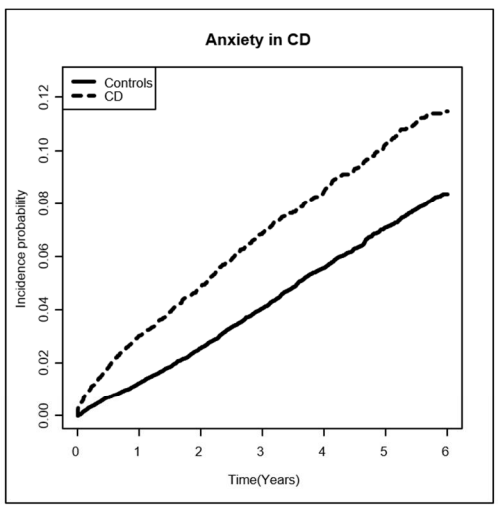
IBD, Inflammatory bowel disease; CD, Crohn’s disease; UC, Ulcerative colitis

Figure 1. Cumulative incidence of anxiety in patients compared to healthy controls.



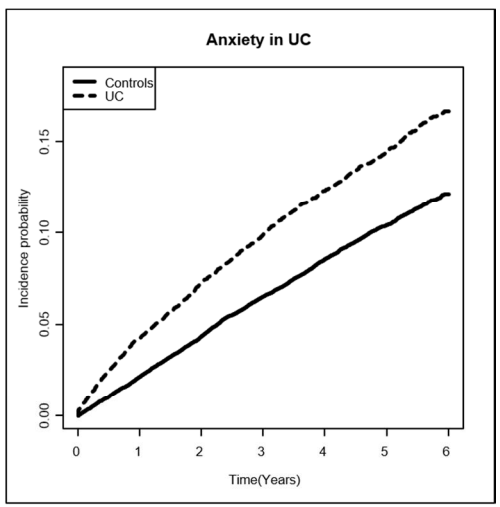
Number at risk

Control	46707	45884	44984	38601	32188	25200	174
IBD	15569	15000	14610	12471	10358	8097	48



Number at risk

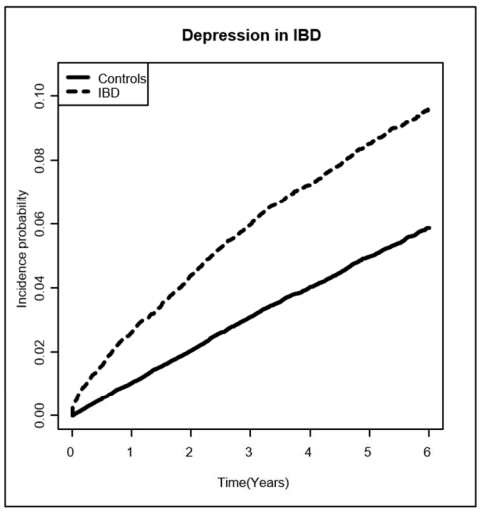
Control	19188	18948	18695	15957	13228	10522
IBD	6396	6210	6090	5167	4274	3399



Number at risk

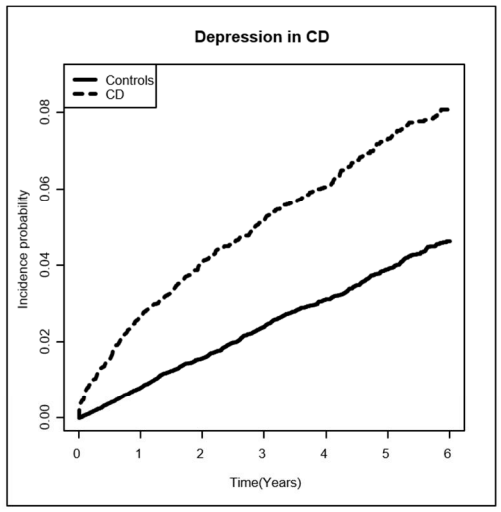
Control	27519	26936	26289	22644	18960	14678	72
IBD	9173	8790	8520	7304	6084	4698	18

Figure 2. Cumulative incidence of depression in patients compared to healthy controls.



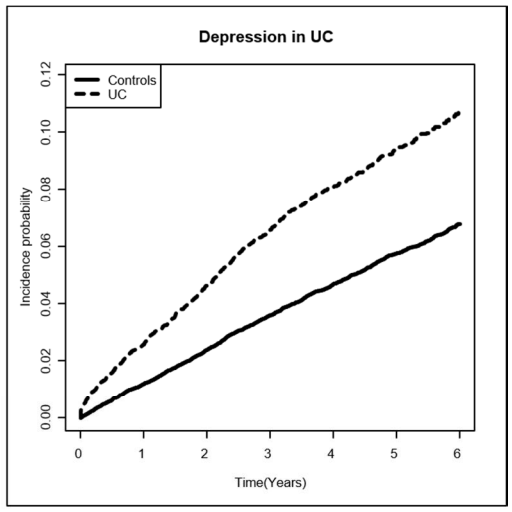
Number at risk

Control	46707	46261	45745	39617	33381	26401	182
IBD	15569	15217	14949	12851	10800	8522	50



Number at risk

Control	19188	19042	18887	16247	13598	10916	102
IBD	6396	6238	6150	5256	4398	3510	31



Number at risk

Control	27519	27219	26858	23370	19783	15485	80
IBD	9173	8979	8799	7595	6402	5012	19

Figure 3. Subgroup analysis of the impact of IBD on developing anxiety.

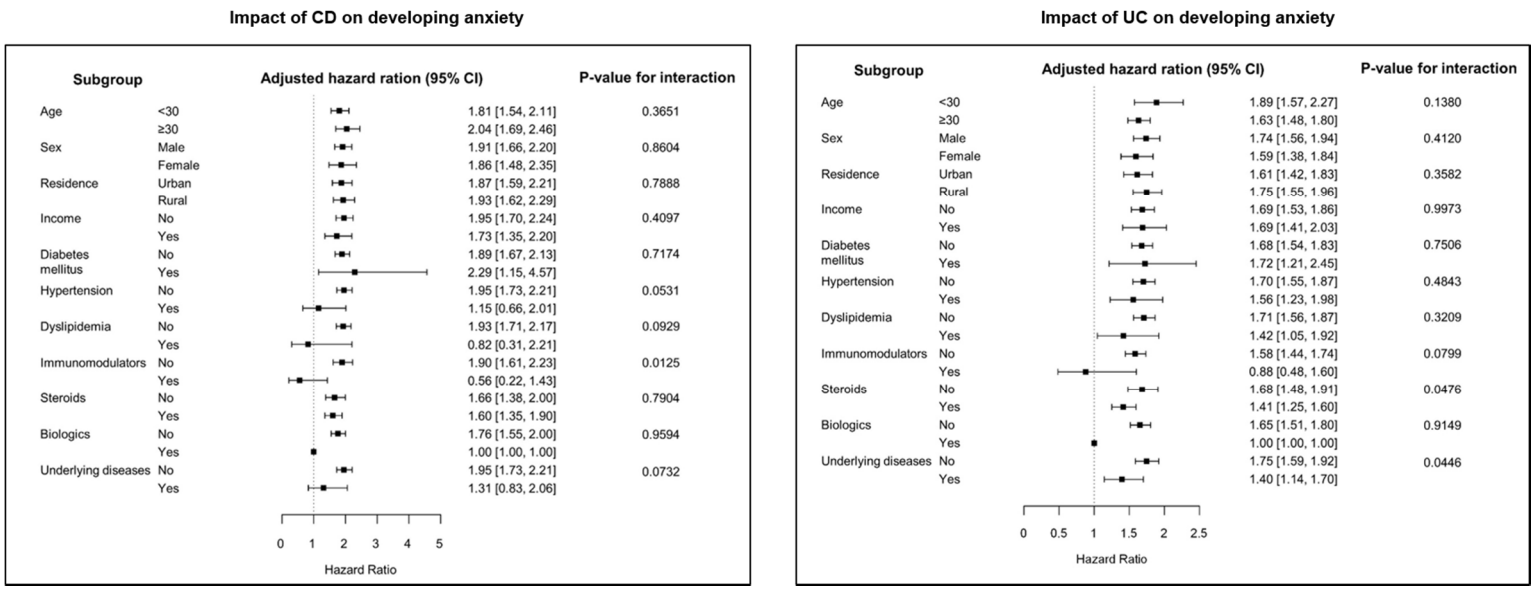
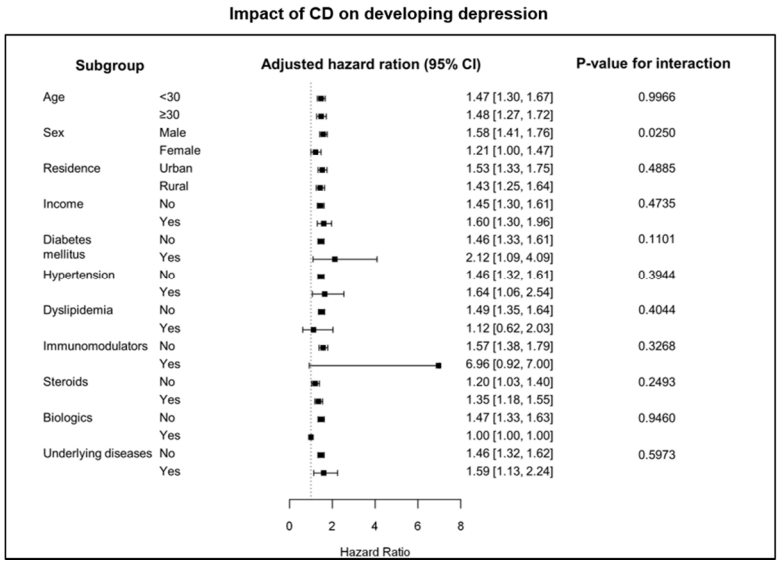
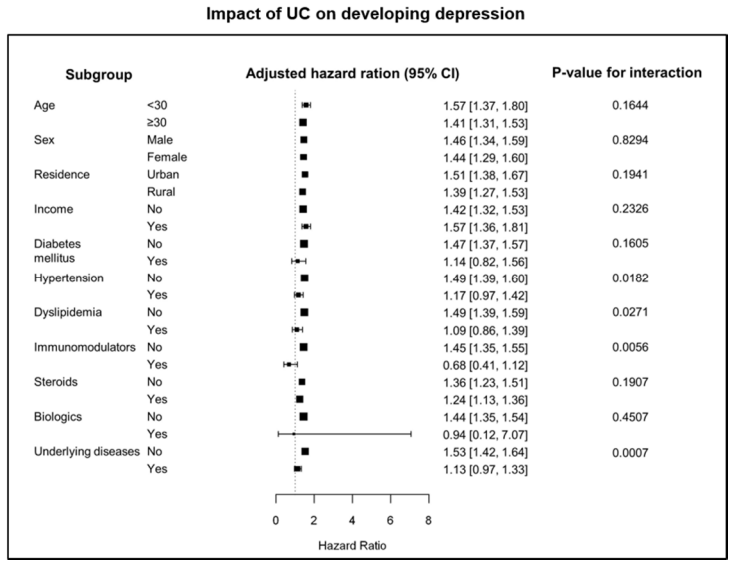


Figure 4. Subgroup analysis of the impact of IBD on developing depression.





Discussion

In this nationwide retrospective cohort study using NHIS database, the risk of anxiety and depression increased in the patients with IBD, respectively. To the best of our knowledge, this study is the first to investigate the risk of anxiety and depression in patients with IBD in Korea. It is consistent with previous studies showing that the incidence of anxiety and depression had a positive relationships with IBD (10, 12, 17, 18). Several hypotheses have been suggested for the high incidence of anxiety and depression in IBD patients. First, IBD patients may have a high psychological stress because of chronic disease course of IBD which repeatedly improves and worsens. Chronic medical conditions were known to cause psychiatric adverse effects and to cause multiple mental illnesses (19-21). Secondly, immunoregulatory pathways which related to inflammatory diseases affect to developing psychological disorders. For example, substance P, a neuropeptide involved in chronic inflammation and in signaling to brain, was significant role in this pathway (22, 23). Finally, therapeutic drug use for IBD may increase the incidence of anxiety and depression. Several previous studies showed that IBD therapeutic drugs, especially steroids, have adverse psychiatric effects which could develop anxiety and depression (24-27). Conversely, studies

have shown that anxiety and depression may be a risk factor for the development of IBD (28-30). It means that mood disorder and IBD can be considered to have mutual influence on their development and disease course.

In Kaplan-Meier curves showing incidence of anxiety and depression in IBD patients (Figure 1, 2), the incidences indicated a steep increase within 1year after diagnosis of IBD. From 1 year after the diagnosis of IBD, the incidence slopes were relatively constant. For possible reason of these results, the first year of IBD diagnosis may be due to not paying much attention to the psychological problems that increase the development of anxiety and depression and after 1 year, psychiatric consultation or treatment may be combined to show a relatively constant increase in incidence.

Subgroup analysis showed that IBD generally appeared to increase the risk of anxiety and depression. However, several confounding factors have been found to increase the risk of anxiety and depression, which is still unclear and needs further study in future.

We conducted several methods to raise the evidence level of this study. First, to reduce misdiagnosis, we limited IBD patients who satisfy both the ICD codes and the RIDs codes. Secondly, by dividing IBD patients into incident

and prevalent group, validation was performed.

This study has several limitations. First, we could not analyze the difference in the risk of depression and anxiety according to the severity of IBD. This was because the NHIS database did not record the severity of IBD. Secondly, this study extracted data from claims data using code for diagnosis, therefore, misdiagnosis or overestimation is possible. Finally, although we showed that the risk of anxiety and depression increases in IBD patients, we could not be able to elucidate its pathologic mechanism and further studies are needed in the future.

In conclusion, the risk of anxiety and depression increased in the patients with IBD, stressing the importance of psychological assessments in IBD patients.

References

1. Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nature reviews Gastroenterology & hepatology. 2015;12(4):205-17.
2. Thia KT, Loftus Jr EV, Sandborn WJ, Yang S-K. An update on the epidemiology of inflammatory bowel disease in Asia. The American journal of gastroenterology. 2008;103(12):3167.
3. Hay AR, Hay JW. Inflammatory bowel disease: medical cost algorithms. Journal of clinical gastroenterology. 1992;14(4):318-27.
4. Addolorato G, Capristo E, Stefanini G, Gasbarrini G. Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. Scandinavian journal of gastroenterology. 1997;32(10):1013-21.
5. Filipović BR, Filipović BF, Kerkez M, Milinić N, Ranđelović T. Depression and anxiety levels in therapy-naive patients with inflammatory bowel disease and cancer of the colon. World journal of gastroenterology: WJG. 2007;13(3):438.
6. Häuser W, Janke KH, Klump B, Hinz A. Anxiety and depression in patients with inflammatory bowel disease: comparisons with chronic liver disease patients and the general population. Inflammatory bowel diseases. 2011;17(2):621-32.
7. Helzer JE, Stillings WA, Chammas S, Norland CC, Alpers DH. A controlled study of the association between ulcerative colitis and psychiatric diagnoses. Digestive diseases and sciences. 1982;27(6):513-8.
8. Kovács Z, Kovács F. Depressive and anxiety symptoms, dysfunctional attitudes and social aspects in irritable bowel syndrome and inflammatory bowel disease. The International Journal of Psychiatry in Medicine. 2007;37(3):245-55.
9. Magni G, Bernasconi G, Mauro P, D'odorico A, Sturniolo G, Canton G, et al. Psychiatric diagnoses in ulcerative colitis. A controlled study. The British Journal of Psychiatry. 1991;158(3):413-5.
10. Nahon S, Lahmek P, Durance C, Olympie A, Lesgourgues B, Colombel JF,

et al. Risk factors of anxiety and depression in inflammatory bowel disease. Inflammatory bowel diseases. 2012;18(11):2086-91.

11. Creed F, Morgan R, Fiddler M, Marshall S, Guthrie E, House A. Depression and anxiety impair health-related quality of life and are associated with increased costs in general medical inpatient. Psychosomatics. 2002;43(4):302-9.

12. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. Inflammatory bowel diseases. 2009;15(7):1105-18.

13. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review. Inflammatory bowel diseases. 2007;13(2):225-34.

14. Kim DS. Introduction: health of the health care system in Korea. Social work in public health. 2010;25(2):127-41.

15. Kim HJ, Hann HJ, Hong SN, Kim KH, Ahn IM, Song JY, et al. Incidence and natural course of inflammatory bowel disease in Korea, 2006–2012: a nationwide population-based study. Inflammatory bowel diseases. 2015;21(3):623-30.

16. Roelen C, Norder G, Koopmans P, Van Rhenen W, Van Der Klink J, Bültmann U. Employees sick-listed with mental disorders: who returns to work and when? Journal of occupational rehabilitation. 2012;22(3):409-17.

17. Graff LA, Walker JR, Lix L, Clara I, Rawsthorne P, Rogala L, et al. The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. Clinical Gastroenterology and Hepatology. 2006;4(12):1491-501. e1.

18. Loftus Jr EV, Guérin A, Andrew PY, Wu EQ, Yang M, Chao J, et al. Increased risks of developing anxiety and depression in young patients with Crohn's disease. The American journal of gastroenterology. 2011;106(9):1670.

19. Katon W, Ciechanowski P. Impact of major depression on chronic

medical illness. Journal of psychosomatic research. 2002;53(4):859-63.
20. Patten SB, Beck CA, Kassam A, Williams JV, Barbui C, Metz LM. Long-term medical conditions and major depression: strength of association for specific conditions in the general population. The Canadian Journal of Psychiatry. 2005;50(4):195-202.
21. Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, Angermeyer M, et al. Depression–anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. Journal of affective disorders. 2007;103(1):113-20.
22. O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. Journal of cellular physiology. 2004;201(2):167-80.
23. Rosenkranz MA. Substance P at the nexus of mind and body in chronic inflammation and affective disorders. Psychological bulletin. 2007;133(6):1007.
24. Cross RK, Lapshin O, Finkelstein J. Patient subjective assessment of drug side effects in inflammatory bowel disease. Journal of clinical gastroenterology. 2008;42(3):244-51.
25. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects. Drug safety. 2000;22(2):111-22.
26. Warrington TP, Bostwick JM, editors. Psychiatric adverse effects of corticosteroids. Mayo Clinic Proceedings; 2006: Elsevier.
27. Yang Y-X, Lichtenstein GR. Corticosteroids in Crohn's disease. The American journal of gastroenterology. 2002;97(4):803.
28. Mardini HE, Kip KE, Wilson JW. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. Digestive diseases and sciences. 2004;49(3):492-7.
29. Mittermaier C, Dejaco C, Waldhoer T, Oefferlbauer-Ernst A, Miehsler W, Beier M, et al. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. Psychosomatic medicine. 2004;66(1):79-84.

30. Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al. The impact of major depressive disorder on the short-and long-term outcome of Crohn's disease treatment with infliximab. Alimentary pharmacology & therapeutics. 2005;22(2):101-10.

국문 초록

배경: 염증성 장질환은 정신과적 질환의 발생과 연관되어 나타날 수 있다. 본 연구의 목적은 염증성 장질환 환자에서 불안증과 우울증의 발생위험도를 분석하는 것이다.

방법: 한국의 국민건강보험공단 데이터베이스를 기반으로 한 청구자료를 이용하여 후향적 연구를 시행하였다. 크론병과 궤양성 대장염 환자는 ICD-10 코드 (K50, K51)와 희귀 난치성 질병 코드 (V130, V131)를 모두 만족하는 케이스로 정의 하였으며, 여기서 희귀 난치성 질병 등록 프로그램은 한국의 희귀 난치성 환자에 대해 약 90% 정도의 의료비용 지원을 해주는 제도이다. 총 15,569명의 염증성 장질환 환자군에 대해 나이와 성별을 매치한 1:3 비율의 비 염증성 장질환 환자군 (대조군) 46,707명을 선정하였다. 전체 연구대상 인구에서 ICD-10 코드를 통하여 불안증과 우울증으로 새롭게 진단받은 환자를 후향적으로 확인하였다. 염증성 장질환 환자에서 불안증과 우울증의 누적 확률을 측정하기 위해 Kaplan-Meier 방법을 사용하였다.

결과: 평균 6년간의 관찰기간 동안, 염증성 장질환 환자는 대조군에 비해 불안증과 우울증을 더욱 자주 경험하는 것으로 확인되었다 (불안증: 12.2% vs. 8.7%, p<0.001; 우울증: 8.0% vs. 4.7%, p<0.001). 크론병 환자에서 불안증의 발생률 (1,000 인년당)은 19.51이었고 대조군에서는 13.26이었으며 (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.40-1.89; p<0.001), 우울증의 발생률은 12.79이었고 대조군에서는 6.6이었다 (HR, 2.09; 95% CI, 1.73-2.52; p<0.001). 궤양성 대장염 환자에서 불안증의 발생률 (1,000 인년당)은 28.9이었고 대조군에서는 19.87이었으며 (HR, 1.60; 95% CI, 1.44-1.77; p<0.001), 우울증의 발생률은 16.49이었고 대조군에서는 9.23이었다 (HR, 2.00; 95% CI, 1.74-2.30; p<0.001). 크론병이 우울증의 발생에 미치는 영향은 남성에서 (adjusted HR, 1.58; 95% CI, 1.41-1.76) 여성에 비해 더 강한 것으로 확인되었다 (adjusted HR, 1.21; 95% CI, 1.00-1.47; p=0.025 by interaction analysis).

결론: 염증성 장질환 환자에서 불안증과 우울증의 발생위험은 모두 상승한다. 따라서 염증성 장질환 환자는 기분장애 발생에 있어

주의 깊은 관찰이 필요하다.