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ORIGINAL ARTICLE

Analysis of the disease activity of ulcerative colitis with and without concomitant primary sclerosing cholangitis: An investigation using a nationwide database in Japan

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Key words
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Abstract

Aims: Primary sclerosing cholangitis (PSC) is a relatively common complication of ulcerative colitis (UC). Only a few studies have investigated the impact of PSC on the clinical course of UC, and their conclusions are contradictory. Therefore, we aimed to compare the disease activity of UC with and without PSC.
Methods and Results: We collected UC patient data using the Diagnosis Procedure Combination database system in Japan and classified eligible admissions into two groups based on their diagnosis of either UC alone or UC associated with PSC. We then compared therapeutic details (medical treatment and surgery) between the two groups. Multivariable logistic regression analysis and propensity score matching was also performed. The rates of systemic steroid injection and infliximab administration in patients with PSC were lower than those in patients without PSC (21% vs. 28%, $P = 0.012$, 9.6% vs. 16%, $P = 0.01$, respectively). The rates of surgery, colorectal cancer, duration of hospital stay, and in-hospital mortality did not differ between the two groups. Multivariable analysis revealed that concomitant PSC was a clinical factor that reduced the odds of systemic steroid injection (odds ratio [OR] = 0.66, 95% confidence interval [CI]: 0.49–0.90, $P = 0.008$) and infliximab (OR = 0.48, 95% CI: 0.32–0.74, $P = 0.0008$) administration.
Conclusion: UC patients with PSC might have less UC disease activity than those with UC alone.

Introduction

Ulcerative colitis (UC) is a diffuse, nonspecific, inflammatory disorder of the colon that mainly affects the mucosa, forming erosions and ulcers.[1,2] UC is sometimes associated with intestinal or extraintestinal manifestations.[1,2] Primary sclerosing cholangitis (PSC) is one such extraintestinal manifestation, characterized by progressive and chronic inflammation of the intra- and/or extrahepatic bile duct. There are no medical treatments for advanced-stage PSC, and several patients with end-stage PSC require liver-transplantation.[3] Although the prevalence of UC in patients with PSC ranges from 26 to 80%,[4–7] only 1.1–7.5% of patients with PSC go on to develop UC.[8–10] Several systematic reviews have demonstrated that the incidence and prevalence of PSC differ geographically.[4,11] Numerous studies have also reported that patients with UC associated with PSC (UC-PSC) tend to have a better UC clinical course than patients with UC alone.[12–14] Conversely, two retrospective studies have found that UC-PSC patients do not have a more benign clinical course.[15,16] However, these reports were mainly from Western countries, and only a small number of single-center case studies have been carried out in Japan[5] and other Asian countries.[9,10,17] The impact of PSC on the clinical course of patients with UC is unclear because of the low prevalence of UC-PSC and its geographic variation. Therefore, the disease activity and clinical course of Japanese UC-PSC patients may differ from that of patients with UC alone.

The Diagnosis Procedure Combination (DPC) is a national database of hospitalizations in Japan.[18] This database has data on a large number of patients and is useful for analyzing rare complications of UC across Japan. Therefore, the UC-PSC association may be better understood by performing an analysis on a large nationwide sample, using the DPC data. Herein, we aimed to investigate the impact of concomitant PSC on the clinical course of patients with UC using a nationwide database in Japan.

Materials and methods

The DPC system. Introduced in 2003, the DPC database is a medical claims database of acute-care hospital admissions in Japan. The system was adopted by 1730 hospitals in 2018, and

covers approximately 83% of the acute-care beds in Japan.[19] The database contains patients' demographics, diagnoses, main disease triggering admission, most resource-consuming diagnosis, comorbidities at admission, complications after admission, medications, surgeries, procedures (including cytapheresis), and condition at discharge.[20–23] Physicians input patient diagnoses into the database according to the International Classification of Diseases, Tenth revision (ICD-10). The DPC database has been used for various clinical studies to date,[24,25] and its diagnostic validity is recognized.[23]

Patients. This study includes the administrative claims data for all inpatients discharged from more than 1000 participating hospitals, as well as for patients with UC who were admitted to DPC-participating hospitals from April 2012 to March 2019. Eligible patients who were admitted to the hospital due to UC were identified by the phrase "ulcerative colitis" included in their most resource-consuming diagnosis within the DPC database. We then classified the eligible patients into two groups: Those with and those without the phrase "primary sclerosing cholangitis disease" in their list of comorbidities at admission, not complications after admission.

Data collection. We collected the following data on patient and clinical characteristics, procedures, and condition at discharge from the DPC database: Patients with the disease name "PSC," age, sex, body mass index (BMI), smoking history (current or ex-smokers vs. non-smokers), the Charlson comorbidity index (CCI),[26] hospital type (academic hospital or not), duration of admission, medication (systemic steroid injection, infliximab, adalimumab, golimumab and vedolizumab, tacrolimus, or tofacitinib), cytapheresis, surgery, in-hospital death, and colorectal cancer complications. We counted admissions, not individual patients, in this study because the DPC database cannot track individuals through different hospitals in the system after referral. Colorectal cancer was identified using the phrase "colon cancer" or "rectal cancer" in the patient disease list. Entries of suspected colorectal cancer, containing the word "suspicious," were excluded.

Data analysis. We classified the eligible patient admissions into two groups according to their age (elderly group: aged ≥65 years, nonelderly group: aged ≤64 years), based on the World Health Organization classification.[27] We also classified the eligible patients into three categories according to their BMI (underweight: < 18.5 kg/m^2, normal range: 18.5–24.9 kg/m^2, and overweight: ≥ 25.0 kg/m^2), based on the World Health Organization classification.[28] The patients' background (sex, average age, BMI, CCI, smoking status, hospital type, and median days of hospital stay), treatment (systemic steroid injections, infliximab, adalimumab, golimumab and vedolizumab, tacrolimus, tofacitinib, cytapheresis, and surgery), and clinical events (colorectal cancer, cholangiocarcinoma, and in-hospital death) were compared between the two groups using chi-squared tests. We also performed a multivariable analysis using logistic regression to identify clinical factors that affected infliximab and systemic steroid injection administration as well as surgery. Clinical factors that included age, sex, BMI, academic hospital or not, and smoking were considered to affect disease severity. Systemic steroid injection was also considered to affect biologics and surgery. Therefore, those factors were selected as variables for the multivariable analysis.

We also conducted propensity score matching analysis to investigate the impact of concomitant PSC on the clinical activity of UC. We used the following variables for propensity score matching: age, sex, BMI, smoking history, and academic hospital or not. We subsequently compared the rates of treatments and clinical events and performed a propensity score matching the same, as described above.

The threshold for statistical significance was $P < 0.05$. All analyses were performed using JMP Pro14 (SAS institute, Tokyo, Japan) software.

Ethical considerations. The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2020-1-325). The requirement for informed consent was waived due to the anonymous nature of the data.

Results

Patient characteristics. We included 79 099 patients in the final analysis, of which 78 838 were assigned to the UC group and the remaining 261 were assigned to the UC-PSC group. Participant characteristics are summarized in Table 1. Statistically significant differences in age, sex, and BMI were observed between the two groups. The average age and BMI of the UC-PSC group was lower than that of the group with UC alone (32.7 years vs. 44.4 years, $P < 0.0001$; 21.0 vs. 20.0, $P = 0.0068$, respectively). The smoking rate in the UC-PSC group was also lower than that in the UC group (19.3% vs. 7.7%, $P < 0.0001$). The rate of admission to academic hospitals in the UC-PSC group was higher than that in the UC group (26.4% vs. 49.0%, $P < 0.0001$). The rate of uncomplicated diabetes in the UC-PSC group was also higher than that in the UC group (10.0% vs. 5.7%, $P = 0.003$). The results after propensity score matching are also shown in Table 1. The standardized difference in each covariable was 0.1. The C-statistics was 0.71.

Comparison of clinical events, medications, and complications. The comparison of clinical events, medications, and complications between the two groups is summarized in Table 2. The rates of systemic steroid injection and infliximab administration in the UC-PSC group were lower than that in the UC group (28% vs. 21%, $P = 0.012$; 21% vs. 15%, $P = 0.01$). In contrast, there were no differences in the rate of cytapheresis, surgery, and in-hospital mortality between the two groups. Although there was no difference in the rate of colorectal cancer between the two groups, the rate of cholangiocarcinoma was significantly higher in the UC-PSC group than in the UC group. The results were similar after propensity score matching (Table 2).

Multivariable analysis for infliximab, systemic steroid injection, and surgery. The results of multivariable analysis for infliximab administration are summarized in Table 3. The clinical factors associated with infliximab administration included female sex (odds ratio [OR] = 0.88, 95% confidence interval [CI]: 0.84–0.92, $P < 0.0001$), younger age (OR = 0.58,

Table 1 Comparison of the clinical characteristics of the study population

	Before propensity score matching ($N = 79\,099$)			After propensity score matching ($N = 492$)			
	UC only ($n = 78\,838$)	UC accompanied with PSC ($n = 261$)	*P*-value	UC only ($n = 246$)	UC accompanied with PSC ($n = 246$)	*P*-value	Standardized difference
Sex (male/female)	**44 564/34 252**	**188/73**	**<0.0001**	177/69	177/69	1	0
Average age (mean ± SD)	**44.4 ± 20.5**	**32.7 ± 17.5**	**<0.0001**	**37.1 ± 19.2**	**31.8 ± 16.6**	**0.0013**	
Age categories							
0–64 years	**62 749**	**239**		224	224	1	0
≥ 65 years	**16 067**	**22**		22	22	1	0
BMI (mean ± SD), kg/m^2	**21.0 ± 5.88**	**20.0 ± 3.27**	**0.0068**	20.3 ± 3.60	19.9 ± 3.28	0.27	0.12
BMI categories							
Overweight (≧25 kg/m^2)	10 457	22		86	86		0
Normal range (18.5–24.9 kg/m^2)	46 033	147		139	139		0
Underweight (<18.5 kg/m^2)	20 083	90		21	21		0
Smoking, *n* (%)	**15 211 (19.3)**	**20 (7.7)**	**<0.0001**	20 (8.1)	20 (8.1)	1	0
Academic hospital, *n* (%)	**20 815 (26.4)**	**128 (49.0)**	**<0.0001**	119 (48)	119 (48)	1	0
Median days of hospital stay (IQR)	16 days (6–29)	17 days (8–30)	0.4				
Charlson Comorbidity Index score			**<0.0001**				
0	59 512	133					
1	13 818	76					
2	4047	24					
Over 3	1476	13					
Acute myocardial infarction, *n* (%)	415 (0.53)	0 (0)	0.24				
Heart failure, *n* (%)	660 (0.84)	3 (1.2)	0.58				
Peripheral vascular disease, *n* (%)	308 (0.39)	1 (0.38)	0.98				
Cerebral vascular disease, *n* (%)	1115 (1.4)	0 (0)	0.05				
Dementia, *n* (%)	367 (0.47)	0 (0)	0.27				
Pulmonary disease, *n* (%)	1847 (2.3)	2 (0.77)	0.09				
Connective tissue disorder, *n* (%)	747 (0.95)	3 (1.2)	0.74				
Peptic ulcer, *n* (%)	7841 (9.9)	33 (12.6)	0.15				
Liver disease, *n* (%)	**1875 (2.4)**	**54 (20.7)**	**<0.0001**				
Diabetes without complications, *n* (%)	**4503 (5.7)**	**26 (10.0)**	**0.003**				
Diabetes with complications, *n* (%)	459 (0.58)	1 (0.38)	0.67				
Paraplegia, *n* (%)	48 (0.06)	0 (0)	0.69				
Renal disease, *n* (%)	483 (0.61)	2 (0.77)	0.75				
Cancer, *n* (%)	**2343 (3.0)**	**14 (5.3)**	**0.02**				
Metastatic cancer, *n* (%)	121 (0.15)	0 (0)	0.53				
Severe liver disease, *n* (%)	**37 (0.05)**	**6 (2.3)**	**<0.0001**				
HIV, *n* (%)	39 (0.05)	0 (0)	0.72				

Bold values means statistical significance.

BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; PSC, primary sclerosing cholangitis; SD, standard deviation; UC, ulcerative colitis.

95% CI: 0.54–0.61, $P < 0.0001$), being overweight (OR = 1.22, 95% CI: 1.15–1.29, $P < 0.0001$), being underweight (OR = 0.86, 95% CI: 0.82–0.90, $P < 0.0001$), admission to an academic hospital (OR = 1.23, 95% CI: 1.17–1.28, $P < 0.0001$), and concomitant PSC (OR = 0.48, 95% CI: 0.32–0.74, $P = 0.0008$).

The results of multivariable analysis for systemic steroid injection are summarized in Table 4. On multivariable analysis, female sex (OR = 0.83, 95% CI: 0.80–0.86, $P < 0.0001$), being elderly (OR = 0.66, 95% CI: 0.63–0.69, $P < 0.0001$), having a higher BMI, nonsmoking, and concomitant PSC (OR = 0.66, 95% CI: 0.49–0.90, $P < 0.0001$) were identified as clinical factors that reduced the risks of systemic steroid injection.

The results of multivariable analysis for surgery are summarized in Table 5. Male sex, being elderly (OR = 1.34, 95% CI: 1.20–1.50, $P < 0.0001$), having a lower BMI (OR = 1.32, 95% CI: 1.19–1.46, $P < 0.0001$), admission to an academic hospital (OR = 3.55, 95% CI: 3.24–3.89, $P < 0.0001$), smoking (OR = 1.41, 95% CI: 1.27–1.57, $P < 0.0001$), systemic steroid injection (OR = 2.37, 95% CI: 2.16–2.59, $P < 0.0001$), and infliximab administration (OR = 0.70, 95% CI: 0.61–0.80, $P < 0.0001$) were identified as the clinical factors that affected surgery rates. Concomitant PSC was not significantly associated with surgery risk.

After propensity score matching, concomitant PSC was identified as a clinical factor associated with infliximab administration (OR = 0.55, 95% CI: 0.32–0.94, $P = 0.03$) (Table 3). However,

Table 2 Comparison of medical treatments, complications, and clinical events in the study population

	Before propensity score matchingTotal ($n = 79\,099$)			After propensity score matching ($n = 492$)		
	UC only ($n = 78\,838$)	UC accompanied with PSC ($n = 261$)	*P*-value	UC only ($n = 246$)	UC accompanied with PSC ($n = 246$)	*P*-value
Systemic steroid injection, *n* (%)	**21 928 (28)**	**55 (21)**	**0.012**	**76 (31)**	**52 (21)**	**0.001**
Biologics, *n* (%)	**16 781 (21)**	**39 (15)**	**0.01**	**56 (22.8)**	**37 (15.0)**	**0.02**
Infliximab, *n* (%)	**13 003 (16)**	**25 (9.6)**	**0.003**	**46 (18.7)**	**24 (9.8)**	**0.004**
Adalimumab, *n* (%)	3023 (3.8)	12 (4.6)	0.41	9 (3.7)	11 (4.5)	0.64
Golimumab, *n* (%)	726 (0.92)	3 (1.2)	0.7	1 (0.4)	3 (1.2)	0.3
Vedolizumab, *n* (%)	185 (0.23)	0 (0)	0.43	1 (0.41)	0 (0)	0.24
Tofacitinib, *n* (%)	208 (0.26)	0 (0)	0.41	1 (0.41)	0 (0)	0.24
Cytapheresis, *n* (%)	12 649 (16)	46 (18)	0.49	45 (18.3)	44 (17.9)	0.9
Surgery, *n* (%)	2504 (3.2)	10 (3.8)	0.34	13 (5.3)	9 (3.7)	0.38
Colorectal cancer, *n* (%)	1437 (1.82)	9 (3.45)	0.08	7 (2.85)	9 (3.66)	0.61
Cholangiocarcinoma, *n* (%)	**12 (0.02)**	**6 (2.3)**	**<0.0001**	**0 (0)**	**5 (2.0)**	**0.008**
In-hospital death, *n* (%)	418 (0.53)	2 (0.77)	0.6	1 (0.41)	2 (0.81)	0.56

Bold values means statistical significance.
PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

concomitant PSC was not identified as a clinical factor that affected systemic steroid injection and surgery rates (Tables 4 and 5).

Discussion

In this study, we compared disease activity between patients with UC-PSC and those with UC alone, using a nationwide database in Japan. Our findings showed that the rates of infliximab administration and systemic steroid injection in UC-PSC patients were lower than those in patients with UC alone. On multivariable analysis, concomitant PSC was found to reduce the odds of infliximab administration and systemic steroid injection, but not the odds of surgery. Several studies have reported contradictory results regarding the impact of PSC on the clinical course of UC.[12,13,15] One reason for this inconsistency might be the relatively small number of patients with UC-PSC included in previous studies. In contrast, our results, using a nationwide database containing a large number of patients, show the differences in medication between the two groups, which indicate milder disease activity in the UC-PSC group compared to the UC group. We also conducted a propensity score-matched analysis and found that the results were similar to those obtained before propensity score matching, highlighting significant

Table 3 Multivariable analysis[†] of the associations between clinical factors and IFX

		Before propensity score matching				After propensity score matching		
Clinical factors	Number of admissions ($n = 79\,099$)	Odds ratio	95% CI	*P*-value	Number of admissions ($n = 492$)	Odds ratio	95% CI	*P*-value
Sex	Male: 44 752	Reference		**<0.0001**	Male: 354	Reference		0.93
	Female: 34 325	**0.88**	**0.84–0.92**		Female: 138	0.98	0.55–1.75	
Age categories	0–64 years: 62 988	Reference		**<0.0001**	0–64 years: 448	Reference		0.75
	≥65 years: 16 111	**0.58**	**0.54–0.61**		≥ 65 years: 44	1.16	0.47–2.90	
BMI categories	Overweight: 10 479	**1.22**	**1.15–1.29**	**<0.0001**	Overweight: 42	0.83	0.30–2.26	0.71
	Normal range: 46 180	Reference			Normal range: 278	Reference		
	Underweight: 20 173	**0.86**	**0.82–0.90**	**<0.0001**	Underweight: 172	0.85	0.61–0.83	0.85
Academic hospital	Yes: 15 231	**1.23**	**1.17–1.28**	**<0.0001**	Yes: 238	1.09	0.65–1.83	0.73
	No: 58 156	Reference			No: 254	Reference		
Smoking	Yes: 15 231	1.02	0.97–1.07	0.52	Yes: 40	0.84	0.30–2.39	0.75
	No: 54 816	Reference			No: 452	Reference		
Systemic steroid injection	Yes: 21 983	0.98	0.94–1.03	0.56	Yes: 128	1.19	0.68–2.10	0.54
	No: 57 116	Reference			No: 364	Reference		
Concomitant PSC	Yes: 261	**0.48**	**0.32–0.74**	**0.0008**	Yes: 246	**0.55**	**0.32–0.94**	**0.03**
	No: 78 838	Reference			No: 246	Reference		

[†]Logistic regression analysis.
Bold values means statistical significance.
BMI, body mass index; CI, confidence interval; IFX, infliximab; PSC, primary sclerosing cholangitis.

Table 4 Multivariable analysis[†] of the associations between clinical factors and systemic steroid injection

		Before propensity score matching				After propensity score matching		
Clinical factors	Number of admissions ($n = 79\,099$)	Odds ratio	95% CI	*P*-value	Number of admissions ($n = 492$)	Odds ratio	95% CI	*P*-value
Sex	Male: 44 752	Reference		**<0.0001**	Male: 354	Reference		0.57
	Female: 34 325	**0.83**	**0.80–0.86**		Female: 138	1.14	0.72–1.81	
Age categories	0–64 years: 62 988	Reference		**<0.0001**	0–64 years: 448	Reference		0.06
	≥ 65 years: 16 111	**0.66**	**0.63–0.69**		≥ 65 years: 44	0.41	0.16–1.03	
BMI categories	Overweight: 10 479	**0.81**	**0.77–0.86**	**<0.0001**	Overweight: 42	0.92	0.41–2.06	0.84
	Normal range: 46 180	Reference			Normal range: 278	Reference		
	Underweight: 20 173	**1.18**	**1.13–1.22**	**<0.0001**	Underweight: 172	1.46	0.94–2.26	0.09
Academic hospital	Yes: 15 231	0.97	0.93–1.01	0.1	Yes: 238	1.32	0.88–2.00	0.18
	No: 58 156	Reference			No: 254	Reference		
Smoking	Yes: 15 231	**1.06**	**1.02–1.11**	**0.003**	Yes: 40	0.63	0.25–1.60	0.33
	No: 54 816	Reference			No: 452	Reference		
Concomitant PSC	Yes: 261	**0.66**	**0.49–0.90**	**0.008**	Yes: 246	0.69	0.45–1.04	0.07
	No: 78 838	Reference			No: 246	Reference		

[†]Logistic regression analysis.
Bold values means statistical significance.
BMI, body mass index; CI, confidence interval; PSC, primary sclerosing cholangitis.

differences in the administration of infliximab between the two groups but not in systemic steroid injections and surgery. According to our results, PSC might have a better effect on the clinical course of UC in Japan.

To our knowledge, this is the first report to demonstrate the improved clinical course of UC-PSC compared to that of UC alone in Japanese patients. However, the DPC database does not contain clinical information such as laboratory data, endoscopic and histological findings, and computed tomography results, which are all useful for directly evaluating UC disease activity. Therefore, we need to establish that database nationwide and conduct a prospective cohort study to evaluate the true effect of PSC on UC disease activity. As the incidence and prevalence of PSC vary geographically,[4,11] more studies from Asian countries are also necessary to evaluate the impact of PSC on the clinical course of UC and to understand geographical differences.

Table 5 Multivariable analysis[†] of the associations between clinical factors and surgery

		Before propensity score matching				After propensity score matching		
Clinical factors	Number of admissions ($n = 79\,099$)	Odds ratio	95% CI	*P*-value	Number of admissions ($n = 492$)	Odds ratio	95% CI	*P*-value
Sex	Male: 44 752	Reference		**<0.0001**	Male: 354	Reference		0.22
	Female: 34 325	**0.77**	**0.70–0.85**		Female: 138	1.8	0.70–4.61	
Age categories	0–64 years: 62 988	Reference		**<0.0001**	0–64 years: 448	Reference		0.18
	≥ 65 years: 16 111	**1.44**	**1.29–1.61**		≥65 years: 44	2.26	0.69–7.42	
BMI categories	Overweight: 10 479	0.91	0.79–1.06	0.23	Overweight: 42	2.02	0.51–7.98	0.32
	Normal range: 46 180	Reference			Normal range: 278	Reference		
	Underweight: 20 173	**1.30**	**1.18–1.44**	**<0.0001**	Underweight: 172	1.4	0.53–3.74	0.5
Academic hospital	Yes: 15 231	**3.52**	**3.21–3.86**	**<0.0001**	Yes: 238	2.28	0.90–5.79	0.08
	No: 58 156	Reference			No: 254	Reference		
Smoking	Yes: 15 231	**1.43**	**1.29–1.60**	**<0.0001**	Yes: 40	2.34	0.63–8.65	0.2
	No: 54 816	Reference			No: 452	Reference		
Systemic steroid injection	Yes: 21 983	**2.38**	**2.17–2.60**	**<0.0001**	Yes: 128	1.38	0.53–3.62	0.51
	No: 57 116	Reference			No: 364	Reference		
IFX	Yes: 21 983	**0.69**	**0.61–0.79**	**<0.0001**	Yes: 70	1.75	0.60–5.11	0.3
	No: 57 116	Reference			No: 422	Reference		
Concomitant PSC	Yes: 261	0.93	0.45–1.90	0.84	Yes: 246	0.7	0.28–1.75	0.45
	No: 78 838	Reference			No: 246	Reference		

[†]Logistic regression analysis.
Bold values means statistical significance.
BMI, body mass index; CI, confidence interval; IFX, infliximab; PSC, primary sclerosing cholangitis.

Although there were significant differences in the rate of administration of systemic steroid injections and infliximab, the rate of surgery between the two groups did not differ. Additionally, concomitant PSC did not affect the surgery rate in multivariable analysis. These contradictions might be because the use of steroids and infliximab prevented the need for surgery. One multicenter, retrospective study reported that surgery rates seem to be decreasing as the use of biologics increases in Japan.[29] On multivariable analysis, our data also showed that infliximab administration reduced the odds of surgery. This result is compatible with previous findings.[29]

Multivariable analysis also showed that elderly patients had lower odds of receiving systemic steroid injections and infliximab, and higher odds of undergoing surgery. Elderly patients are likely to develop complications, such as infection, with commonly used immunosuppressive therapies.[30,31] Therefore, physicians might prefer surgery over strong immunosuppressive agents when treating elderly patients in the early stages of worsening UC.

There were significant differences in several CCI diseases, including liver disease, uncomplicated diabetes, cancer, and severe liver disease, between the two groups. Liver disease and severe liver disease were presumed to be detected by the presence of PSC in this study. In contrast, no correlation was found between PSC and diabetes mellitus. One multicenter retrospective study reported a correlation of PSC with diabetes,[32] wherein the risk of type 1 diabetes was increased in PSC patients, but the risk of type 2 diabetes was not increased.[32] We hypothesized that as both PSC and type 1 diabetes are autoimmune diseases, they may be likely to develop concomitantly. A single-center retrospective study has also reported the increased risk of other autoimmune diseases in PSC.[33] PSC is also associated with an increased risk of cholangiocarcinoma.[3] Our data showed a significant increase in cholangiocarcinoma, but no increase in colorectal cancer, in the UC-PSC group. These results are compatible with those previously reported. However, the total number of patients with cancer in each group was not equivalent with the numbers of cholangiocarcinoma and colorectal cancer. Therefore, another malignancy should be suspected. Patients with two or more autoimmune diseases such as UC-PSC might be likely to develop several malignancies. The odds of surgery due to dysplasia and colorectal cancer in UC-PSC might be higher, while the odds of surgery due to severe and uncontrolled UC might be lower. However, we were not able to identify the reasons of surgery because the DPC database does not contain information of the reason for surgery.

This study had several limitations. First, we selected patients who were hospitalized with a diagnosis of UC. However, whether these patients were hospitalized for the purpose of UC treatment was unclear. Nevertheless, the diagnostic validity of the DPC database has been previously recognized.[23] Eligible patients were also determined according to whether UC was listed as the disease for which the most medical resources were administered, to increase the accuracy as much as possible (However, some patients, for instance, that were primarily diagnosed with PSC and later diagnosed with UC as comorbidity might be missed.). Furthermore, the large sample size of this study supported the performance of statistical analysis. Second, as mentioned above, the DPC database does not contain information on patient conditions such as age at disease onset, disease duration, endoscopic and pathological findings, laboratory data, and computed tomography findings. Therefore, we evaluated disease severity by investigating the therapeutic agents used and the surgery rate. Third, the DPC database targets in-hospital patients only, and the DPC-participating hospitals were typically acute-care, relatively large-volume hospitals. As our study focused on admitted patients and not out-patients, the data did not necessarily reflect all UC-PSC patients. The prevalence of UC-PSC in our data was lower (0.33%) than that in previous reports (1.1–7.5%).[8–10] This discrepancy reflects the hypothesis that patients with UC-PSC are less likely to require hospital admission because of lower disease activity; therefore, more UC-PSC cases might have been present among the out-patients excluded from this analysis.

Furthermore, the DPC database cannot track individuals through different hospitals in the system. Therefore, we counted admissions, not individual patients, in this study. We also could not obtain long-term follow-up data.

This is a retrospective study, which is also a limitation. Despite these limitations, the DPC database allowed us to collect and analyze data from a large number of patients, which is useful for the investigation of rare diseases and complications such as PSC associated with UC.

In conclusion, UC patients with PSC might have lower UC disease activity than patients with UC alone. A nationwide prospective cohort study is warranted to clarify the impact of PSC on the clinical course of UC.

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