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The Impact of Concomitant Ulcerative Colitis on the Clinical Course in Patients with Primary Sclerosing Cholangitis: An Investigation Using a Nationwide Database in Japan

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Keywords
Ulcerative colitis · Primary sclerosing cholangitis · Liver transplantation · Biliary drainage · Cholangiocarcinoma

Abstract
Introoduction: Primary sclerosing cholangitis (PSC) is a rare disease, especially in Asian countries. PSC often develops during ulcerative colitis (UC). Little is known about the severity of PSC in patients with UC. Thus, this study aimed to investigate the impact of concomitant UC on the clinical course of patients with PSC using a nationwide database in Japan. ***Methods:*** We collected data on patients who were admitted for PSC using a nationwide database and divided eligible admissions according to concomitant UC (PSC-UC group vs. PSC-alone group). We conducted propensity score matching and compared the rates of liver transplantation, biliary drainage, and other clinical events between the two groups. We also conducted a multivariate analysis to identify the clinical factors that affect biliary drainage, cholangiocarcinoma, and liver transplantation. ***Results:*** We enrolled 672 patients after propensity score matching. The rate of liver transplantation in the PSC-UC group was lower than that in the PSC-alone group (2.2 vs. 5.4%, $p = 0.002$), whereas the rate of biliary drainage did not differ between the two groups (38.1 vs. 33.8%, $p = 0.10$). On multivariate analysis, concomitant UC was identified as a clinical factor that decreased the risk of liver transplantation (odds ratio = 0.40, 95% confidence interval: 0.23–0.68, $p = 0.0007$). ***Discussion:*** Concomitant UC in patients with PSC may decrease the risk of liver transplantation. The milder disease activity of PSC with UC is more likely compared to that of PSC without UC.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with repeated exacerbation and remission of unknown etiology and sometimes develops several extraintestinal manifestations (EIMs) [1, 2]. Primary sclerosing cholangitis (PSC) is a rare EIM of UC and is defined as a chronic cholestatic liver disease characterized by lesions in the intra- and/or extrahepatic bile duct [3].

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There are no curative treatments for critical PSC, and several patients with end-stage PSC require liver transplantation [3].

As described above, PSC is a rare EIM of UC, with reports that PSC is diagnosed in 0.8–5.6% of patients with UC [3, 4]. In contrast, 50–80% of patients with PSC had UC in Northern Europe and the USA [5–8], whereas the incidence of PSC in healthy controls was 2% in the UK [8]. These studies indicate that PSC and UC are expected to have a strong relationship and have the potential to affect each other's clinical course. Several studies have reported that the clinical course of UC associated with PSC is better than that of UC alone [9–14]. However, little is known about the impact of concomitant UC on the clinical course of PSC. The low incidence of PSC, even in the general population [6], especially in Eastern countries [15], makes analyses difficult because of the small number of samples in a single center. Moreover, the studies described above were mostly from Western countries. The influence of UC on PSC should be investigated in clinical practice.

The diagnosis procedure combination (DPC) database is a nationwide database of hospitalizations in Japan, which contains data from a large number of patients and is useful for analyzing rare diseases, including PSC. Therefore, the PSC-UC association may be better understood by performing an analysis of a large nationwide sample using DPC data. To date, clinical studies have been conducted using the DPC database [14, 16–19]. This study aimed to investigate the impact of concomitant UC on the clinical course of patients with PSC, using a nationwide database in Japan.

Materials and Methods

DPC System

The DPC database, introduced in 2003, is a medical claims database of acute-care hospital admissions in Japan. The system was adopted by 1,764 hospitals in 2022 and covers approximately 85% of the acute care beds (approximately 480,000 beds) in Japan [20] . The DPC database contains patient demographics, medications, surgeries, procedures (including endoscopic and percutaneous biliary drainage), and condition at discharge [21–24]. Disease diagnosis was categorized as "main diagnosis," "main disease triggering admission," "most resource-consuming diagnosis," "second-most resource-consuming diagnosis," "comorbidities at admission," and "complications after admission." Physicians input these patient diagnoses into the database according to the International Classification of Diseases, Tenth Revision (ICD-10). The diagnostic validity of UC using ICD-10 has been recognized [25, 26]. The DPC database cannot track the same patients if they are transferred to another hospital. Therefore, in this study, we extracted eligible admissions, instead of counting individuals.

Extraction of Eligible Admissions

This study included administrative claims data for all inpatients discharged from more than 1,000 participating hospitals, as well as for patients with PSC who were admitted to DPC-participating hospitals from April 2012 to March 2020. Eligible admissions due to PSC were identified as those with the phrase "primary sclerosing cholangitis disease (ICD-10 code: K830)" in one of the following categories in the DPC database: "main diagnosis," "main disease triggering admission," or "most resource-consuming diagnosis." We then classified the eligible admissions into two groups: those with and without the phrase "ulcerative colitis" in their list of comorbidities at admission (Fig. 1).

Data Collection

We collected the following data on patient and clinical characteristics, procedures, and conditions at discharge from the DPC database: age, sex, body mass index (BMI), smoking history (current or ex-smokers vs. nonsmokers), Charlson comorbidity index (CCI) [27], hospital type (academic hospital or not), duration of admission, in-hospital death, cancer (cholangiocarcinoma [CCA], colorectal cancer [CRC]) in any of the disease list, systemic steroid injection, biliary drainage (endoscopic stent insertion, endoscopic nasobiliary drainage, and percutaneous drainage), liver transplantation, and surgery for malignancy (hepatectomy, pancreaticoduodenectomy, hepatic hilar bile duct malignant tumor resection). CRC was identified using the phrase "colon cancer" or "rectal cancer" in the patient's disease list. In addition, any disease name that contained the word "suspicious" was excluded.

Data Analysis

Eligible admissions were divided into two groups, with and without concomitant UC (PSC-UC group vs. PSC-alone group). We also classified the eligible admissions into two categories according to their age (elderly, aged ≥65 years; nonelderly, aged ≤64 years) based on the World Health Organization (WHO) classification [28]. We also classified the eligible admissions 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 WHO classification [29]. The patients' background (sex, average age, BMI, CCI, smoking status, hospital type, and median days of hospital stay), treatments (biliary drainage, surgery, and liver transplantation), comorbidities (CRC and CCA), and clinical events (in-hospital death) were compared between the two groups using χ^2 tests. We also performed multivariate analysis using logistic regression to identify the clinical factors affecting drainage and transplantation procedures. Clinical factors, including age, sex, BMI, academic hospital, and smoking, were considered to affect disease severity. Systemic steroid injections have also been considered to affect the efficacy of biologics and surgery [1]. Therefore, these factors were selected as variables for the multivariable analysis.

We also performed a propensity score matching analysis to determine the effect of concomitant UC on the clinical activity of PSC. The following variables were used for propensity score matching: age, sex, BMI, smoking history, hospital type, and CCI. We calculated the C-statistics and standardized differences for each variable described earlier when we conducted propensity score matching. C-statistics are preferable if they are over 0.7. After matching, the two groups were comparable for all standardized differences <0.1. After propensity score matching, we compared

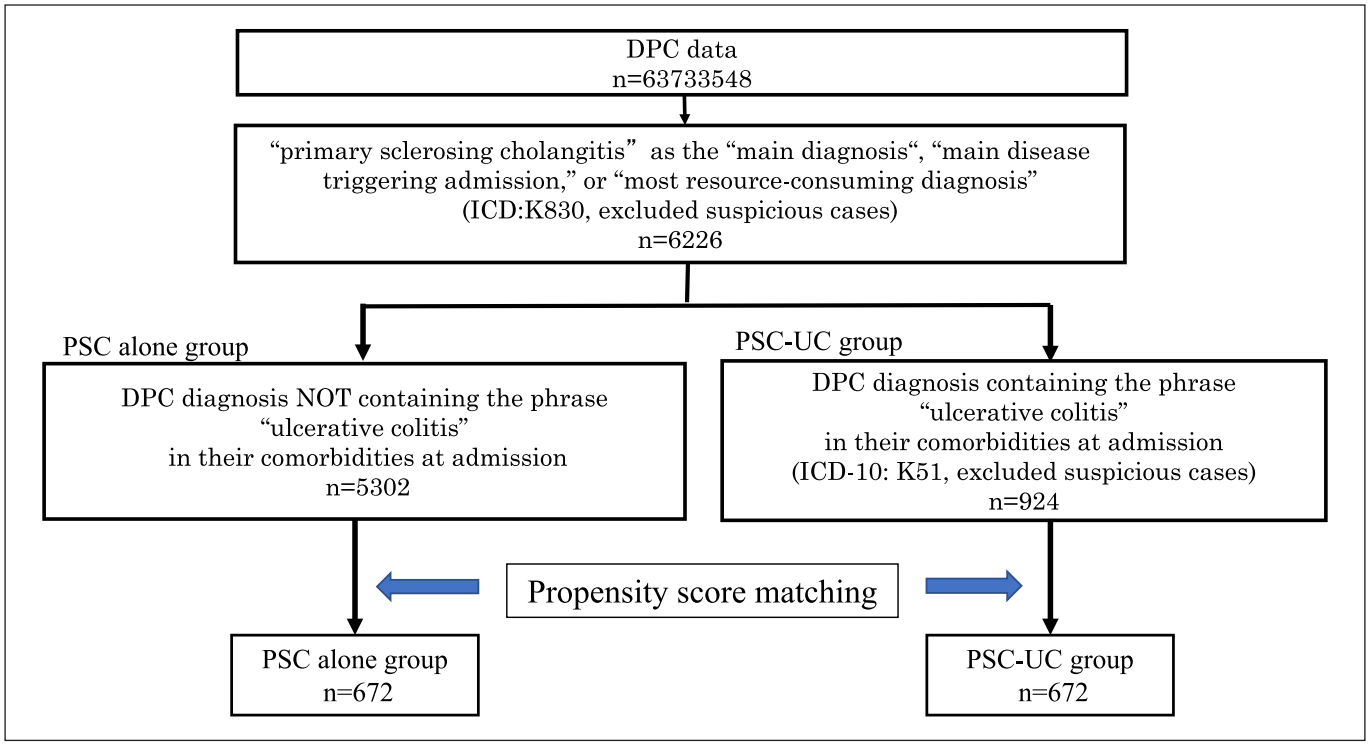

Fig. 1. Study flowchart. The eligible admissions were extracted from the database as per this flowchart.

the treatments, comorbidities, length of hospital stay, and clinical events between the two groups.

The threshold for statistical significance was set at $p < 0.05$. All analyses were performed using the JMP Pro14 software (SAS Institute, Tokyo, Japan).

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2020-1-325). The requirement for informed consent was waived because of the anonymity of the data.

Results

Patients' Backgrounds

The background of eligible admissions is summarized in Table 1. We eventually included 6,226 eligible admissions, of which 924 were assigned to the PSC-UC group and the remaining 5,302 to the PSC-alone group. After propensity score matching, 672 pairs were selected, and there were no differences in background characteristics between the two groups. The C-statistic was 0.90, and the standardized difference for each variable was <0.1.

Comparison of Treatments, Comorbidities, and Clinical Events

The results of the comparison between the two groups are summarized in Table 2. Before propensity score matching, the rates of concomitant CCA and in-hospital death in the PSC-UC group were significantly lower than those in the PSC-alone group (2.3 vs. 4.4%, $p = 0.0019$; 1.7 vs. 3.9%, $p = 0.0004$). After propensity score matching, the liver transplantation rate in the PSC-UC group was significantly lower than that in the PSC-alone group (2.2 vs. 5.4%, $p = 0.002$).

Multivariate Analysis for Biliary Drainage, CCA, and Liver Transplantation

The results of multivariate analysis of drainage are summarized in Table 3. Female sex was identified as a clinical factor that decreased the risk of biliary drainage (odds ratio [OR] = 0.80, 95% confidence interval [CI]: 0.71–0.88, $p < 0.0001$). Conversely, older age was identified as a clinical factor that increased the risk of biliary drainage (OR = 1.48, 95% CI: 1.33–1.66, $p < 0.0001$). Concomitant UC has not been identified as a clinical factor affecting the risk of biliary drainage.

Table 1. Comparison of the clinical characteristics of the study population between before and after propensity score matching

	Before propensity score matching (total, *n* = 6,226)			After propensity score matching (total, *n* = 1,344)			
	PSC-alone group (*n* = 5,302)	PSC-UC group (*n* = 924)	*p* value	PSC only (*n* = 672)	PSC-UC group (*n* = 672)	*p* value	standardized difference
Sex (male/female)	2939/2447	572/265	**<0.0001**	470/202	445/227	0.14	0.08
Mean age, years	59.9 (SD 19.9)	38.4 (SD 16.8)	**<0.0001**	44.0 (SD 0.69)	39.3 (SD 0.69)	**<0.0001**	
Age categories			**<0.0001**			0.74	
0–64 years	2,630	752		594	590		0.02
Over 65 years	2,759	85		82	82		0
BMI (mean± SD), kg/m^2	**21.4±3.5**	**20.9±3.6**	**0.0008**	21.0±0.14	20.7±0.14	0.19	
BMI categories			**0.0002**			0.78	
Overweight (over 25.0 kg/m^2)	725	101		72	68		0.02
Normal range (18.5–24.9 kg/m^2)	3,558	512		421	416		0.02
Underweight (below 18.5 kg/m^2)	1010	214		169	181		0.04
CCI							
Acute myocardial infarction, *n* (%)	16 (0.3)	2 (0.2)	0.77	0 (0)	2 (0.3)	0.1	
Heart failure, *n* (%)	**126 (2.3)**	**5 (0.60)**	**0.0002**	4 (0.6)	5 (0.67)	0.74	
Peripheral vascular disease, *n* (%)	27 (0.50)	1 (0.12)	0.07	0 (0)	0 (0.1)	0.24	
Cerebral vascular disease, *n* (%)	**81 (1.50)**	**2 (0.43)**	**0.0004**	0 (0)	2 (0.3)	0.1	
Dementia, *n* (%)	**75 (1.39)**	**3 (0.36)**	**0.004**	2 (0.3)	3 (0.45)	0.65	
Pulmonary disease, *n* (%)	149 (2.76)	14 (1.67)	0.05	9 (1.3)	13 (1.9)	0.39	
Connective tissue disorder, *n* (%)	64 (1.19)	5 (0.60)	0.1	8 (1.2)	5 (0.74)	0.4	
Peptic ulcer, *n* (%)	363 (6.74)	52 (6.21)	0.57	51 (7.6)	46 (6.6)	0.46	
Liver disease, *n* (%)	**1191 (22.1)**	**238 (28.4)**	**<0.0001**	176 (26)	196 (29)	0.22	
Diabetes without complication, *n* (%)	**593 (11)**	**44 (5.3)**	**<0.0001**	43 (6.4)	34 (5.1)	0.29	
Diabetes with complication, *n* (%)	**73 (1.35)**	**2 (0.24)**	**0.001**	4 (0.6)	2 (0.3)	0.41	
Paraplegia, *n* (%)	2 (0.04)	0 (0)	0.44	1 (0.15)	0 (0)	0.24	
Renal disease, *n* (%)	67 (1.24)	5 (0.60)	0.08	11 (1.6)	4 (0.3)	0.06	
Cancer, *n* (%)	**439 (8.15)**	**38 (4.54)**	**0.0001**	25(3.7)	32 (4.8)	0.34	
Metastatic cancer, *n* (%)	**21 (0.4)**	**0 (0)**	**0.014**	2 (0.3)	0 (0)	0.25	
Severe liver disease, *n* (%)	293 (5.44)	49 (5.85)	0.63	46 (6.9)	44 (6.6)	0.83	
HIV, *n* (%)	0 (0)	0 (0)					
CCI score			0.27			0.60	
0	3147	40		376	365		
1	1740	19		195	196		
2	608	4		37	49		
Over 3	656	12		64	62		
Smoking (%)	**1,039 (19)**	**109 (13)**	**<0.0001**	104 (15)	100 (15)	0.76	0
Academic hospital (%)	**2,228 (41)**	**489 (59)**	**<0.0001**	431 (64)	416 (62)	0.40	0.05

DPC, diagnosis procedure combination; UC, ulcerative colitis; PSC, primary sclerosing cholangitis; SD, standard deviation; BMI, body mass index; AIDS, acquired immunodeficiency syndrome.

Regarding CCA, only older age was identified as a clinical factor that increased the risk (OR = 2.45, 95% CI: 1.82–3.28, $p < 0.0001$). Other factors that affected the risk of CCA were not identified as clinical factors.

Multivariate analysis also showed the clinical factors that affected the risk of liver transplantation. Concomitant UC (OR = 0.40, 95% CI: 0.23–0.68, $p = 0.0007$) and elderly age (OR = 0.04, 95% CI: 0.01–0.13, $p < 0.0001$) were identified as clinical factors that decreased the risk of liver transplantation. Conversely, underweight (OR = 2.03, 95% CI: 1.40–2.97, $p = 0.0003$) and academic hospitals (OR = 15.2, 95% CI: 7.10–32.8, $p < 0.0001$) were identified as clinical factors that increased the risk of liver transplantation.

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

	Before propensity score matching (total, *n* = 6,226)			After propensity score matching (total, *n* = 1,344)		
	PSC-alone group (*n* = 5,302)	PSC-UC group (*n* = 924)	*p* value	PSC-alone group (*n* = 672)	PSC-UC group (*n* = 672)	*p* value
Biliary drainage, *n* (%)	2,225 (41.3)	331 (2556)	0.34	227 (33.8)	256 (38.1)	0.10
Liver transplantation, *n* (%)	120 (2.2)	16 (1.9)	0.55	**36 (5.4)**	**15 (2.2)**	**0.002**
CCA, *n* (%)	**237 (4.4)**	**19 (2.3)**	**0.0019**	17 (2.5)	14 (2.1)	0.59
Colorectal carcinoma, *n* (%)	40 (0.7)	9 (1.1)	0.33	4 (0.6)	8 (1.2)	0.24
Surgery for malignancy, *n* (%)	14 (0.26)	1 (0.1)	0.33	1 (0.15)	1 (0.15)	1
In-hospital death, *n* (%)	**210 (3.9)**	**14 (1.7)**	**0.0004**	19 (2.8)	13 (1.9)	0.28
Median days of hospital stay (IQR)	**9 (5–17)**	**8 (5–14)**	**0.0017**	**8 (5–17)**	**8 (5–15)**	**0.02**

Bile duct drainage: the following combined: "percutaneous transluminal bile duct drainage, ENBD, endoscopic stent insertion." Surgery for malignancy: the following combined: "hepatectomy, pancreaticoduodenectomy, hepatic hilar bile duct malignant tumor surgery." UC, ulcerative colitis; PSC, primary sclerosing cholangitis; IQR, interquartile range.

Discussion

We investigated the impact of concomitant UC in patients with PSC by comparing treatment outcomes and clinical events using a DPC database. We also conducted multivariate analysis to identify the factors that affect the clinical course and activity of PSC. After propensity score matching, the rate of liver transplantation in the PSC-UC group was lower than that in the PSC-alone group. On multivariate analysis, our results also showed that concomitant UC was a clinical factor that decreased the risk of liver transplantation. However, our analysis did not show whether concomitant UC is related to the risk of biliary drainage and CCA.

After propensity score matching, the PSC-UC group demonstrated a lower rate of liver transplantation than the PSC-alone group. Multivariate analysis using the data before propensity score matching also revealed that concomitant UC decreased the OR for liver transplantation. To the best of our knowledge, this is the first study to demonstrate a lower risk of liver transplantation in patients with PSC-UC than in those with PSC alone. Although a retrospective single-center study reported a tendency for a lower rate of liver transplantation (including candidacy) in the PSC-UC group than in the PSC-alone group, there was no statistical difference between the two groups [30]. This may be because this study included a relatively small number of patients. In contrast, our study, which included a large number of cases, was able to identify the difference between the two groups. However, another study reported no association between concomitant UC and the rate of liver transplantation [13]. Several reports have described differences in the incidence and clinical course of UC and PSC between Western and Eastern countries [15, 31, 32]. Although our study included a large number of patients, its design was retrospective. Further prospective studies in Asian countries are warranted.

The DPC database does not include detailed clinical information such as endoscopic findings, laboratory data, computed tomography, and magnetic resonance imaging. Biliary drainage was selected as an indicator of PSC disease activity in this study. This study did not show a difference in the rate of biliary drainage between the two groups and demonstrated that concomitant UC was not associated with the risk of biliary drainage in multivariate analysis. These results indicate that the disease activity of PSC is not different, regardless of concomitant UC. We previously reported a study regarding the impact of concomitant PSC in patients with UC [14], whose relationship was opposite to that of this study. Our previous study indicated that UC patients with PSC might have lower UC disease activity than patients with UC alone. Conversely, the results of this study did not demonstrate such differences in disease activity between the PSC-UC and PSC-alone groups. The discrepancy between the results of biliary drainage and liver transplantation might be due to the low rate of liver transplantation in Japan. Liver transplantation is the only curative treatment for PSC. A multicenter survey reported that only 12% of patients undergo liver transplantation in Japan [33]. In Japan, the annual number of liver transplantation was only around 400 cases [34, 35]. The number of liver transplantation in other

Table 3. Multivariate analysis of the association between clinical factors and three endpoints (biliary drainage, CCA, and liver transplantation)

Clinical factors	Patients, $n = 6,226$	Biliary drainage			CCA			Liver transplantation		
		OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender	Male: 3,511	Reference		**<0.0001**	Reference		0.72	Reference		0.89
	Female: 2,712	**0.80**	**0.71–0.88**		0.95	0.72–1.25		1.03	0.71–1.48	
Age categories	0–64 years: 3,382	Reference		**<0.0001**	Reference		**<0.0001**	Reference		**<0.0001**
	Over 65 years: 2,844	**1.48**	**1.33–1.66**		**2.45**	**1.82–3.28**		**0.04**	**0.01–0.13**	
BMI categories	Overweight: 826	1.05	0.90–1.22	0.55	0.53	0.33–0.85	0.0088	0.58	0.28–1.16	0.12
	Normal range: 4,070	Reference			Reference			Reference		
	Underweight: 1,224	0.91	0.80–1.03	0.15	0.93	0.67–1.29	0.64	**2.03**	**1.40–2.97**	**0.0003**
Academic hospital	Yes: 2,717	1.09	0.98–1.22	0.11	1.08	0.82–1.72	0.59	**15.2**	**7.10–32.8**	**<0.0001**
	No: 3,509	Reference			Reference			Reference		
Smoking	Yes: 1,148	0.96	0.98–1.21	0.58	1.22	0.89–1.69	0.22	1.37	0.84-2.25	0.21
	No: 5,078	Reference			Reference			Reference		
Concomitant UC	Yes: 837	1.05	0.90–1.23	0.56	0.75	0.46–1.23	0.26	**0.40**	**0.23–0.68**	**0.0007**
	No: 5,389	Reference			Reference			Reference		

UC, ulcerative colitis; PSC, primary sclerosing cholangitis; BMI, body mass index.

Asian countries including India and Korea were higher than that in Japan. Furthermore, the annual number of liver transplantation in the USA was about 8,000 cases in 2017 (source of information: http://www.transplant-observatory.org) (last accessed December 30, 2022). This small number of liver transplantation in Japan may lead to our results of low rate of liver transplantation. Palliative endoscopic or percutaneous biliary drainage should be performed instead of liver transplantation. As previously described, biliary drainage was selected as an indicator of PSC severity. Such palliative biliary drainage may not reflect the severity of PSC. We must conduct a prospective study to precisely evaluate the disease severity of PSC.

As PSC progresses, there is a risk of developing liver cirrhosis, CCA, and/or CRCs [36]. Our analysis did not demonstrate a difference in the rates of CCA and surgery, which are suspected to be related to CCA. Moreover, the rate of CRC did not differ between PSC-UC group and UC-alone group. Several studies from Asian countries have reported no difference in the rates of CRC between PSC-UC group and UC-alone group [30, 37]. On the contrary, a retrospective study from Japan reported that the rate of CCA in PSC-UC group was higher than that in UC-alone group [30]. The risk of malignancy in patients with PSC-UC is inconsistent. There may be geographical and genetic differences in the development of malignant tumors between Western and Eastern countries, as well as in the incidence of PSC.

This study has some limitations. First, the DPC database does not contain detailed patient information, including laboratory data and endoscopic and radiological findings, which are useful for evaluating the severity of PSC. Therefore, we indirectly evaluated the disease severity by investigating the rates of liver transplantation and biliary drainage. Second, the DPC database mainly includes data of in-hospital patients, not out-hospital patients, and cannot identify the same patients referred to another hospital. The number of admissions was counted. Moreover, our study design was cross-sectional owing to the nature of the DPC database. However, prospective or retrospective cohort studies are preferable for analyzing chronic diseases, such as PSC and IBD. Furthermore, selection bias is one of the limitations of this study. Our study design limited to inpatients who are expected to be more severe than outpatients. Another study using a database which was different from the DPC reported that 14.1% of patients with UC were hospitalized at onset [38]. We need to conduct a prospective cohort study or a retrospective study which includes outpatients' data to eliminate selection bias. Third, we cannot deny the existence of confounding factors derived from the design of this study

even though propensity score matching was performed. Fourth, the validity of PSC using ICD-10 is not completely confirmed [39]. However, another study described that the new PSC-specific ICD-10 code released in 2018 could deal with this issue [40]. Further investigations of validating for UC using ICD-10 code are warranted. Although this study has some limitations, the DPC database contains a large number of admissions, which enables us to analyze rare diseases and comorbidities.

In conclusion, concomitant UC in patients with PSC may decrease the risk of liver transplantation, although the risk of biliary drainage was not different regardless of the presence of concomitant UC. The milder disease activity of PSC with UC is more likely compared to that of PSC without UC. Further prospective studies are warranted to clarify the effect of concomitant UC on the clinical course of PSC.

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Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2020-1-325).The requirement for written informed consent was waived because of the anonymity of the data. This decision was approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2020-1-325).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.M., K.Y., K.T., Y.S., T.N., H.S., and Y. Kakuta contributed to the study conception and design. Material preparation, data collection, and analysis were performed by R.M., K.T., K. Fujimori, and K. Fushimi. The first draft of the manuscript was written by R.M. and revised critically by S.H., Y. Kunouchi, and A.M. All authors read and approved the final version of the manuscript.

Data Availability Statement

Data cannot be shared with researchers who are not approved to access them by the Japanese Ministry of Health, Labour and Welfare. Further inquiries can be directed to the corresponding author.

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