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ORIGINAL ARTICLE

Severity of acute pancreatitis in patients with inflammatory bowel disease in the era of biologics: A propensity-score-matched analysis using a nationwide database in Japan

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Abstract

Background and Aim: Acute pancreatitis (AP) is a rare extraintestinal manifestation of inflammatory bowel disease (IBD). Several studies from Western countries have reported that the severity of AP in patients with IBD is similar to that in the general population; however, its severity in patients from Eastern countries in the era of biologics remains unclear. This study aimed to investigate the severity of AP in patients with IBD and the effect of biologics on the severity of AP using a nationwide database.
Methods: We divided 1138 eligible AP admissions from the Diagnosis Procedure Combination database system into IBD and non-IBD groups after propensity score matching, and compared the severity of AP. We divided the IBD group into ulcerative colitis (UC) and Crohn's disease (CD) subgroups and compared each with the non-IBD group. Logistic regression analysis was conducted to identify the clinical factors affecting acute pancreatitis.
Results: IBD and UC groups had lower rate of severe AP compared to the non-IBD group (13.7% *vs* 28.3%, $P < 0.0001$ and 11.0% *vs* 28.3%, $P < 0.0001$, respectively). There were no differences in the rates of severe AP between the CD and non-IBD groups. Multivariate analysis showed that biologics did not affect the severity of AP.
Conclusion: The severity of AP in patients with IBD may be lower than that in the general population; biologics for IBD may not worsen its severity. Further prospective studies are required to clarify the severity of AP in patients with IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder that mainly affects the intestine and is characterized by repeat exacerbations and remissions; its etiology remains unknown.[1,2] Further, IBD develops various extraintestinal manifestations (EIMs) including arthritis, pyoderma gangrenosum, primary sclerosing cholangitis, thrombosis, and uveitis.[3,4] Acute pancreatitis (AP) is one of the rare EIMs, and a study with a follow-up period of 10 years reported its frequency in patients with Crohn's disease (CD) at 1.4%.[5] Another study reported that the incidence of AP in IBD patients at 1.6%.[6] However, a population-based study indicated that the incidence of AP in the IBD population was 3.56-fold higher than that in the comparison

cohort.[7] Several studies have also reported that the severity and clinical course of AP are similar to those in the general population.[6,8–10] However, these studies were reported from Western countries and investigated in the pre-biologics era. Even though there are a few studies from Eastern countries, whether biologics could worsen the severity of AP remains unclear. Clarifying these aspects is necessary in clinical practice. However, it is difficult to collect enough cases to evaluate AP in IBD cohorts from a single center.

There is a national claims database for hospitalization in Japan, named the Diagnosis Procedure Combination (DPC). The DPC database contains data for a large number of admissions.[11] This database has been used to conduct investigations targeting primary sclerosing cholangitis as a rare EIM of UC[12] in elderly patients with UC[13] and to evaluate a clinical guideline for AP[14] with sufficient data. Moreover, propensity (PS)-score-matched analyses have been performed to evaluate the efficacy of metallic stents for obstructive colorectal cancers and urgent colonoscopy for colonic diverticular bleeding using the same database.[15,16] The DPC database enabled the evaluation of AP in the IBD population owing to its high volume of data.

This study aimed to evaluate the impact of IBD on the severity and clinical course of AP using a nationwide database in Japan. We also investigated whether biologics could affect the severity of AP in patients with IBD.

Methods

DPC data system. The DPC database was introduced in 2003 as a medical claims database for inpatient and acute-care hospitals in Japan. It covered approximately 83% of acute-care beds in 1730 hospitals in 2018.[17] There are six distinct categories of diagnosis, namely "main diagnosis," "main disease triggering admission," "most resource-consuming diagnosis," "second most resource-consuming diagnosis," "comorbidities at admission," and "complications after admission," in the DPC database. Furthermore, the DPC database contains patient demographics, medical costs, severity of AP, procedures (including the use of mechanical ventilator, admission to intensive care unit, and dialysis), and condition at discharge (death or not). The validity of disease names using ICD-10 codes has been confirmed.[11,18,19]

DPC data system, Extraction of eligible admissions and data collection, Data analysis, Statistics, and Ethics.

Extraction of eligible admissions and data collection. We collected administrative claims data for all patients admitted to and subsequently discharged from more than 1100 DPC-participating hospitals from July 2014 through March 2021 for AP. AP was identified using the ICD-10 code K85 for the most resource-consuming diagnosis. Entries of suspicious cases containing the word "suspicious" were excluded. We also collected additional information on comorbidities of IBD, including UC and CD, at admission.

We collected the following data on patients from the DPC database: age, sex, body mass index (BMI), smoking history, Charlson comorbidity index (CCI),[20] hospital type (academic hospital or not), condition at discharge (in-hospital death), medical costs (available data from 2016 to 2020), length of hospital stay, and procedures (artificial ventilation, dialysis, and admission to the intensive care unit). Information regarding the administration of 5-amynosalicylic acid (5ASA), azathioprine, and biologics including infliximab, adalimumab, ustekinumab, vedolizumab, and golimumab during 3 months before admission for AP was also collected. Data regarding the severity of AP, which was evaluated at admission according to the Japanese severity criteria[21] (Table S1, Supporting information), were also collected. Physicians entered the most severe computed tomography (CT) grade data and prognostic factors during admission in the DPC database, and the severity of AP was assessed based on these data. The patients were divided into two groups (mild and severe) depending upon AP severity. A nationwide epidemiological survey in Japan demonstrated that the mortality rate increased according to prognostic factor scores of this criteria.[22]

Data analysis. We divided the eligible AP admissions with and without concomitant IBD into the IBD and non-IBD groups, respectively. We also classified the enrolled patients into five categories according to their age (≤49 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years) and into three categories according to BMI (underweight: <18.5 kg/m^2, normal range: 18.5–24.9 kg/m^2, overweight: >25.0 kg/m^2) based on the World Health Organization classification. We conducted a PS-matching analysis to evaluate the impact of concomitant IBD on the clinical course of AP. We used the following variables for PS matching: sex, age and BMI categories as described above, CCI, smoking history, and hospital type. We subsequently compared the IBD and non-IBD groups using rates of severe AP, in-hospital death, use of mechanical ventilation, admission to the intensive care unit, and dialysis, using chi-square tests, and the length of hospitalization and medical costs of hospital stay, using Wilcoxon's signed-rank test. After PS matching, the IBD group was divided into two subgroups (CD and UC groups). We then compared the rates of severe AP, in-hospital death, use of mechanical ventilation, admission to the intensive care unit, dialysis, length of hospitalization, and medical costs of hospital stay among the subgroups and the non-IBD group. We also performed a multivariate logistic regression analysis with the data before PS matching to identify the clinical factors that affect AP severity.

Statistics. The threshold for statistical significance was set at $P < 0.05$. All analyses were performed using the JMP Pro16 software (SAS Institute, Tokyo, Japan). We calculated the *C*-statistics and standardized differences for each variable described above when we conducted PS matching.

Ethics. The study protocol was reviewed and approved by the Ethics Committee of the Tohoku University Graduate School of Medicine (2021–1–815). The requirement for informed consent was waived because of the anonymity of the data.

Results

Backgrounds of study population. We excluded cases in which data of CT grade and prognostic factors were defective (n = 31 431), and cases that had both CD and UC as comorbidities at time of admission (n = 1). Finally, 123 848 patients

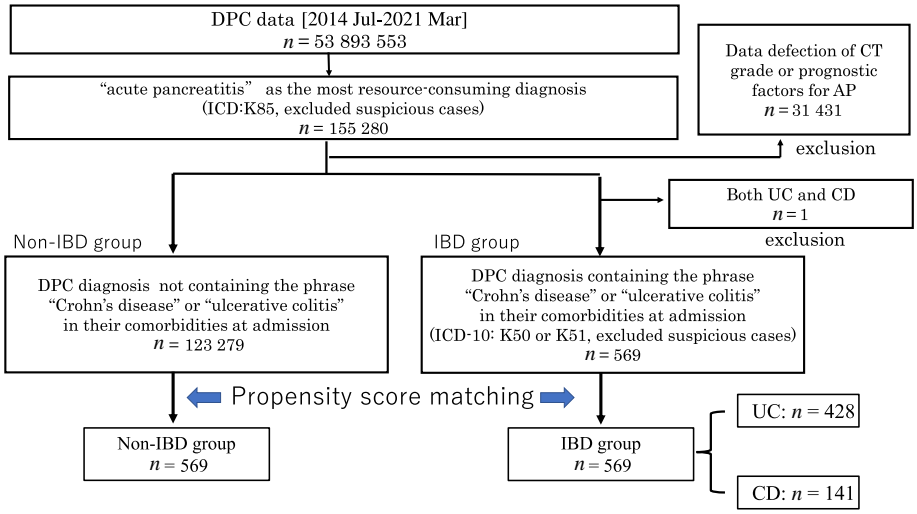

Figure 1 Study flowchart. The eligible admissions were extracted from the database as per this chart. Admissions without available data for prognostic factors or computed tomography grade were excluded. One admission that had both ulcerative colitis and Crohn's disease as comorbidities at the time of admission was also excluded. After propensity score matching, we eventually divided the patients into the inflammatory bowel disease and non-IBD groups; each group contained 569 patients.

were included, of whom 569 were assigned to the IBD group and the remaining 123 279 to the non-IBD group (Fig. 1). After PS matching, 569 pairs of admissions were selected. The *C*-statistic was 0.78, and the standardized difference for each variable was <0.1. The characteristics of the study population are summarized in Table 1. The characteristics of both the groups were similar after PS matching.

Comparisons of clinical outcomes between non-IBD and IBD groups. Comparisons of the clinical outcomes between the non-IBD and IBD groups after PS matching are summarized in Table 2. The occurrence of severe AP in the IBD group was significantly lower than that in the non-IBD group (13.7% *vs* 28.3%, $P < 0.0001$). The rate of use of mechanical ventilator in the IBD group was also significantly lower than that in the non-IBD group (0.70% *vs* 2.6%, $P = 0.018$). In contrast, the length of hospital stay in the IBD group was longer than that in the non-IBD group (11 *vs* 10 days, $P = 0.0048$).

Comparisons of clinical outcomes between non-IBD and UC/CD groups. Comparisons of the clinical outcomes between the non-IBD and UC groups are summarized in Table 3. The occurrence of severe AP in the UC group was significantly lower than that in the non-IBD group (11.0% *vs* 28.3%, $P < 0.0001$). The rates of use of mechanical ventilation and dialysis in the UC group were also lower than those in the non-IBD group (0.47% *vs* 2.6%, $P = 0.011$ and 0.23% *vs* 2.1%, $P = 0.0095$, respectively). The length of hospital stay in the UC group was longer than that in the non-IBD group (11 *vs* 10 days, $P = 0.0063$).

There were no differences in the clinical outcomes between the CD and non-IBD groups (Table 4).

Multivariate analysis for severe AP in IBD group. The results of multivariate analysis of the association between clinical factors and AP severity in the IBD group are summarized in Table 5. On multivariate analysis, the use of azathioprine within 3 months before admission due to AP was identified as a clinical factor that decreased the severity of AP. Two points or more of CCI was identified as a clinical factor that increased AP severity. The use of 5-ASA and biologics within 3months before admission due to AP was not identified as a clinical factor that affected the development of severe AP.

Discussion

We investigated the influence of concomitant IBD on the clinical course and severity of AP by using a nationwide database in Japan. Our analysis using PS matching revealed a lower occurrence of severe AP in patients with IBD than in those without IBD. Furthermore, the incidence of dialysis and use of mechanical ventilation in patients with UC was lower than that in patients without IBD. On multivariate analysis, use of 5ASA and biologics was not identified as a clinical factor that affected the development of severe AP.

Our results demonstrate a lower incidence of severe AP in patients with IBD than in those without IBD. Our results also showed that the incidence of mechanical ventilation use and dialysis in the IBD group was statistically lower than in the non-IBD group. These results also support the lower severity of AP in the IBD group than in the non-IBD group. To the best of our knowledge, our study is the first to statistically report a lower severity of AP in patients with IBD. Several studies have reported that the severity of AP in patients with IBD is similar to that in patients without IBD.[6,8–10] These studies were conducted in Western countries with a relatively small number of patients and were reported in the pre-biologics era. In contrast, our study from an Eastern country had a large number of cases of AP with IBD. Furthermore, this study targeted admissions in the era after the approval of biologics for IBD treatment. In Japan, infliximab was

Table 1 Comparison of backgrounds of study population between before and after propensity score matching

	Before propensity score matching			After propensity score matching			
	Total $n = 123\,848$			Total $n = 1138$			
	Non-IBD group $n = 123\,279$	IBD group $n = 569$	*P*-value	Non-IBD group $n = 569$	IBD group $n = 569$	*P*-value	Standardized difference
Sex (male/female)	100 873/53 673	518/216	**0.0012**	410/159	410/159	1.00	0
Mean age (SD), years	61.2 (18.7)	42.5 (17.9)	**<0.0001**	44.7 (17.7)	42.4 (17.9)	0.013	
Age categories			**<0.0001**			1.00	
≥80 years	22 637	13		13	13		0
70–79 years	23 936	37		37	37		0
60–69 years	20 807	56		56	56		0
50–59 years	18 938	76		76	76		0
≤49 years	34 990	378		378	378		0
Mean body mass index (SD), kg/m^2	22.8 (4.7)	21.9 (4.6)	**<0.0001**	22.0 (4.1)	21.9 (4.6)	0.29	
BMI categories			**<0.0001**			1.00	
Overweight (>25.0 kg/m^2)	30 245	106		106	106		0
Normal range (18.5–24.9 kg/m^2)	69 068	339		339	339		0
Underweight (<18.5 kg/m^2)	15 461	109		109	109		0
Charlson comorbidity index score (SD)	0.74 (1.1)	0.35 (0.68)	**<0.0001**	0.36 (0.76)	0.35 (0.68)	0.99	0.014
Smoking history (yes/no)	51 688/50 508	174/330	**<0.0001**	174/330	174/330	1.00	0
Academic hospital (yes/no)	12 055/111 224	121/448	**<0.0001**	121/448	121/448	1.00	0
						C-statistics	0.78

Note: The bold value means statistical significance.

Table 2 Comparison of clinical outcomes between non-IBD and IBD groups

Clinical outcomes	After propensity score matching Total ($n = 1138$)		
	Non-IBD group ($n = 569$)	IBD group ($n = 569$)	*P*-value
Severe AP, *n* (%)	161 (28.3%)	78 (13.7%)	**<0.0001***
In-hospital deaths, *n* (%)	4 (0.70%)	3 (0.53%)	1.00*
Usage of mechanical ventilator, *n* (%)	15 (2.6%)	4 (0.70%)	**0.018***
Admission to intensive care unit, *n* (%)	14 (2.5%)	8 (1.4%)	0.28*
Dialysis, *n* (%)	12 (2.1%)	6 (1.1%)	0.23*
Median days of hospital stay (interquartile range), days	10 (7–15)	11 (8–16)	**0.0048****
Median medical costs of hospital stay (interquartile range), JPY	462 884 (338 580–702 190)	486 002 (359 610–699 195)	0.0503**

*Chi-square test.
**Median test.
AP, acute pancreatitis; JPY, Japanese Yen.
Note: The bold value means statistical significance.

Table 3 Comparison of clinical outcomes between non-IBD and UC group

Clinical outcomes	After propensity score matching excluding CD cases Total ($n = 997$)		
	Non-IBD group ($n = 569$)	UC group ($n = 428$)	*P* value
Severe AP, *n* (%)	161 (28.3%)	47 (11.0%)	**<0.0001***
In-hospital death, *n* (%)	4 (0.70%)	0 (0%)	0.14*
Usage of mechanical ventilator, *n* (%)	15 (2.6%)	2 (0.47%)	**0.011***
Usage of intensive care unit, *n* (%)	14 (2.5%)	6 (1.4%)	0.26*
Dialysis, *n* (%)	12 (2.1%)	1 (0.23%)	**0.0095***
Median days of hospital stay (interquartile range), days	10 (7–15)	11 (8–17)	**0.0063****
Median medical costs of hospital stay (interquartile range), JPY	462 884 (338 580–702 190)	484 120 (358 664–704 753.5)	0.18**

*Chi-square test.
**Median test.
AP, acute pancreatitis; CD, Crohn's disease; JPY, Japanese Yen; UC, ulcerative colitis.
Note: The bold value means statistical significance.

Table 4 Comparison of clinical outcomes between non-IBD and CD group

Clinical outcomes	After propensity score matching excluding UC cases Total ($n = 710$)		
	Non-IBD group ($n = 569$)	CD group ($n = 141$)	*P*-value
Severe AP, *n* (%)	161 (28.3%)	31 (22.0%)	0.14*
In-hospital death, *n* (%)	4 (0.70%)	3 (2.1%)	0.14*
Usage of mechanical ventilator, *n* (%)	15 (2.6%)	2 (1.4%)	0.55*
Admission to intensive care unit, *n* (%)	14 (2.5%)	2 (1.4%)	0.75*
Dialysis, *n* (%)	12 (2.1%)	5 (3.6%)	0.35*
Median days of hospital stay (interquartile range), days	10 (7–15)	11 (9–16)	0.13**
Median medical costs of hospital stay (interquartile range), JPY	462 884 (338 580–702 190)	505 072 (362 009–684 207)	0.11**

*Chi-square test.
**Median test.
AP, acute pancreatitis; CD, Crohn's disease; JPY, Japanese Yen; UC, ulcerative colitis.

Table 5 Multivariate analysis[†] of the association between clinical factors and severe AP in IBD group

Clinical factors	Number of patients (before propensity score matching)	Severe AP		
		Odds ratio	95% CI	*P*-value
Sex	Male: 410	Reference		0.85
	Female: 159	0.94	0.52–1.72	
Age categories	≥80 years: 13	0.77	0.15–4.01	0.75
	70–79 years: 37	0.71	0.23–2.20	0.56
	60–69 years: 56	1.06	0.47–2.41	0.89
	50–59 years: 76	1.30	0.63–2.68	0.48
	<50 years: 378	Reference		
BMI classification	Overweight: 106	1.55	0.82–2.93	0.18
	Normal: 339	Reference		
	Underweight: 109	1.32	0.69–2.50	0.40
Smoking history	Yes: 174	0.96	0.53–1.75	0.90
	No: 330	Reference		
Academic hospital	Yes: 121	1.33	0.74–2.38	0.34
	No: 448	Reference		
Chralson comorbidity index score	0: 422	Reference		
	1: 107	0.90	0.45–1.80	0.76
	≥2: 40	**2.40**	**1.04–5.53**	**0.040**
Usage of biologics within 3 months before developing AP	Yes: 43	2.45	0.98–6.11	0.054
	No: 526	Reference		
Usage of azathioprine within 3 months before developing AP	Yes: 121	**0.22**	**0.084–0.58**	**0.0023**
	No: 448	Reference		
Usage of 5-ASA within 3 months before developing AP	Yes: 275	0.66	0.39–1.12	0.12
	No: 294	Reference		

[†]Logistic regression analysis.
AP, acute pancreatitis; CI, confidence interval.
Note: The bold value means statistical significance.

first approved for the treatment of CD by insurance in 2002 and for maintenance therapy in 2007. Other biologics have also been approved and widely used for IBD in clinical practice. However, the influence of biologics on AP severity and clinical course remains unclear. Our multivariate analysis demonstrated that the use of biologics and 5ASA was not a clinical factor that affected the severity of AP in patients with IBD. Our results indicate that biologics may not be a risk factor that worsens AP. The results of our study indicate that the severity of AP in IBD is less than that in non-IBD patients, even in the era of biologics.

The reason for the lower severity of AP in patients remains unclear. Several studies have reported that the risk of AP increases in IBD patients.[7,23,24] The pathogenesis of AP in patients with IBD varies, including gallstones, autoimmune mechanisms, drug-induced types including azathioprine and 5ASA, duodenal stenosis due to intestinal inflammation, and anatomical abnormalities.[10,25–29] A multicenter cohort study reported that drug-induced AP was the most common form of AP, followed by idiopathic AP.[30] A systematic review reported that most cases associated with azathioprine and 6-mercaptopurine in CD patients were of mild severity and resolved upon cessation of drugs.[27] Furthermore, our multivariate analysis for severe AP pointed to a lower odds ratio of azathioprine usage, which is compatible with that review. This may be one of the reasons for the mild severity of AP in patients with IBD. Most cases of idiopathic AP are reported to be mild.[30] These studies could explain the reason for mild AP in IBD patients.

Gallstones is one of the most frequent causes of AP in IBD patients.[31] The risk of gallstones in patients with CD is almost double that in the general population.[32,33] Several patients with gallstone pancreatitis undergo endoscopic retrograde pancreatography and endoscopic sphincterotomy. The higher incidence of gallstone-induced AP, which is likely to require endoscopic intervention, might contribute to the lower AP severity in patients with IBD. Furthermore, two studies have reported that serum levels of tumor necrosis α (TNFα) are elevated during AP.[34,35] Our multivariate analysis demonstrated that the use of biologics was not a clinical factor affecting severe AP. Alternatively, immunosuppressive treatments for IBD might eventually decrease the serum levels of TNFα and contribute to the lower severity of AP. These two hypotheses may also explain the lower AP severity in patients with IBD.

We divided the IBD group into UC and CD groups and compared them with the non-IBD group. Although the incidence of severe AP in the UC group was lower than that in the non-IBD group, no differences were observed between the CD and non-IBD groups. However, a review reported that the severity and prognosis of AP in patients with CD are the same as those in the general population.[36] This finding is consistent with our results. The severity of AP in patients with CD is not worse than that in the general population. Our data contained a smaller number of CD cases than UC cases. This might be one of the reasons why there were no differences in AP severity between the CD and non-IBD groups. The reasons for the smaller number of CD

cases than UC cases in our data were unclear. A Japanese nationwide survey reported that the number of patients with UC is three times higher than those with CD.[37] The UC-to-CD ratio in our data was also ~3. This might a reason for the smaller number of CD cases in our data.

The median days of hospital stay were longer by 1 day in patients with UC than those in patients without IBD. Its meaning in clinical practice is unclear. The medical costs between the UC and non-IBD group were not different. Therefore, the difference in the length of hospital stay may not depend on the difference in AP severity between the two groups. There may be some relevant missing information that affects the length of hospital stay. Further investigation is warranted.

This study had several limitations. First, the DPC database depends on the ICD-10 code accuracy. However, the validity of the ICD-10 codes has been confirmed in several studies.[11,18] Second, the DPC database does not contain details of the patients' condition or information including laboratory data, which are useful for identifying the severity of AP. We evaluated the severity of AP based on the Japanese severity criteria,[21] the data for which were entered into the DPC database by physicians. Third, the AP etiology was unclear because of the nature of the DPC database. As described above, AP is developed by various causes. The difference of etiology of AP may affect the severity of AP. Clarifying the etiology of AP is essential to precisely analyze and understand the severity of AP in patients with IBD. Fourth, the DPC database cannot distinguish between patients if they move to another hospital. Therefore, we extracted data pertaining to eligible admissions rather than patients. The DPC database contains a large number of cases that are useful and effective for analyzing rare complications associated with IBD. A nationwide prospective study is needed to confirm the results of this study and resolve the limitations described above.

Conclusion

In conclusion, the severity of AP in patients with IBD may be lower than that in the general population. The use of biologics may not affect the clinical course of inpatients with AP and IBD. However, this was a retrospective study, although our analysis contained a large number of cases. We need to conduct a prospective nationwide study to evaluate the severity of AP in patients with IBD and effects of the use of biologics more precisely, and address the limitations of this study.

Data availability statement. The authors elect not to share the data.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Severity criteria for acute pancreatitis proposed by the Japanese Ministry of Health, Labor and Welfare 2008.