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ORIGINAL ARTICLE

Potential drug-induced constipation: A retrospective study using a Japanese claims database

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Key words
database research, drug-induced constipation, laxative, opioid-induced constipation, symptomatic constipation.

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Abstract

Background and Aim: Detailed clinical information regarding drug-induced constipation (DIC) is limited. This study aimed to investigate the real-world situation of DIC.
Methods: This retrospective study used data from a Japanese claims database registered from 2014 to 2021. The constipation cohort included subjects with at least one record of treated constipation, while the non-constipation cohort was selected through random stratified sampling method, to match the constipation cohort by gender. The study population and control with at least one history of a known causative drug (CD) were matched 1:1 using propensity scores. The proportion of potential DIC (pDIC), the timing of diagnosis for pDIC, and the proportion of prescriptions by drug class for both the CDs and the laxatives were calculated, while logistic regression analysis was performed to explore additional associated factors.
Results: Of the 4 533 905 subjects, 178 852 were eligible in both the study population and the control. The pDIC group comprised of 19 485 patients, which accounted for 10.9% of all treated constipation subjects, while the non-constipation with CD group had 10 430 subjects. The median duration between the recorded CD prescription and treated constipation was 38.0 days. The most frequently prescribed CD was cardiovascular drugs (47.9%). All CD classes, being male, and some comorbidities were associated with the occurrence of pDIC.
Conclusion: The pDIC subjects accounted for about 11% of all treated constipation cases. Since DIC requires different treatment regimens compared to other constipation types, physicians should be cognizant to provide patients with optimized treatments.

Introduction

Constipation is one of the most common gastrointestinal symptoms, with a reported prevalence of 15.3–17.1% in the general population in Europe and Oceania.[1] In Japan, the overall prevalence of constipation is 3.5%, with a higher rate of 6.9% among the population aged 65 years and over.[2] Nowadays, constipation is considered an important public health issue.[1,3] It is associated with various diseases,[4–7] affects prognosis,[8,9] and negatively impacts patients' quality of life[10] and labor productivity.[11]

Constipation is generally classified into two types: primary and secondary constipation.[12] The former includes functional constipation and irritable bowel syndrome with predominant constipation, and the latter is related to multiple factors such as medication (drug-induced constipation [DIC]), various diseases (symptomatic constipation), and colonic disorders (constipation caused by organic diseases). Improvements in lifestyle and pharmacotherapy are recommended for the treatment of these types of constipation, except constipation caused by organic diseases, which should be managed by treating the primary disease.

DIC is one of the secondary types of constipation in which causative drug (CD) administration should be considered as the first step in the treatment strategy, as DIC may reduce compliance with therapy,[13] resulting in discontinued treatment of the targeted disease. However, in cases where the CD is essential for

treating the primary disease, it cannot be reduced or discontinued. Opioid-induced constipation (OIC) is the most representative DIC and globally well-known. According to the international classification of constipation Rome IV, the definition of OIC is independent of functional constipation (FC), stressing the difficulty of distinguishing OIC from FC due to their overlap in clinical practice.[14] Considering that opioid use is relatively less frequent in Japan compared to other developed countries,[15] other CDs may have a greater impact on DIC in Japan. Guidelines for chronic constipation have identified 12 CD classes.[16] However, the proportion of these drugs causing DIC in clinical practice and the impact of each drug class on DIC is unknown.

The purpose of this study is to investigate the proportion of potential DIC (pDIC) among all constipation patients who require therapeutic intervention, the proportion of prescribed CDs and laxative drugs (LDs), and the factors associated with the occurrence of pDIC.

Methods

Data source. This is a retrospective observational study using a Japanese healthcare database maintained by MinaCare Corporation (Tokyo, Japan). This database is an employment-based health insurance database that includes periodically updated health-checkup data and medical/pharmaceutical claims data of company employees and their dependent family members, which covers a large scale of personal health information nationwide. Health-checkup data include information on subjects' clinical laboratory test results and health status questionnaires such as smoking status, exercise habits, and eating and alcohol consumption habits. We used the largest identifiable population in the MinaCare database, which includes 4 533 905 individuals insured between 1 April 2014 and 31 March 2021.

Study design. The eligible subjects were categorized as follows. All subjects: All individuals insured during the data period from April 2014 to March 2021. Constipation cohort: Patients with at least one record of constipation disease codes (Table S1, Supporting information), except the constipation codes that may be given with a diagnosis clearly different from DIC, such as pediatric, maternal, psychogenic, habitual, postoperative, dietary, rectal constipation, and constipation associated with organic disease. Non-constipation cohort: Insured individuals without a constipation record were selected randomly by stratified sampling so that the gender composition was the same as the constipation cohort, since constipation has been reported to be associated with gender.[17]

Study population: Patients in the constipation cohort with at least one record of constipation and at least one record of a laxative prescription (hereinafter, LD, Table S2). The index date was defined as the date of the first prescription of the drug that can lead to DIC (hereinafter, CD, Table S3) during the study period (Fig. 1). Control: Patients in the non-constipation cohort who were prescribed a CD. For subjects who were prescribed a CD, the index date was defined similarly to the study population; for the subjects who were not prescribed a CD, the index date was 3 months before the date of the latest record available. The study population and control were matched by propensity score according to their age and gender,[1,2,17–19] since constipation has been reported to be associated with these characteristics. The following subjects were excluded: (i) Subjects with organic diseases that can cause constipation (Fig. 1), or subjects with any record of an organic disease (Table S4) during the year before the index date were excluded from both the constipation and the non-

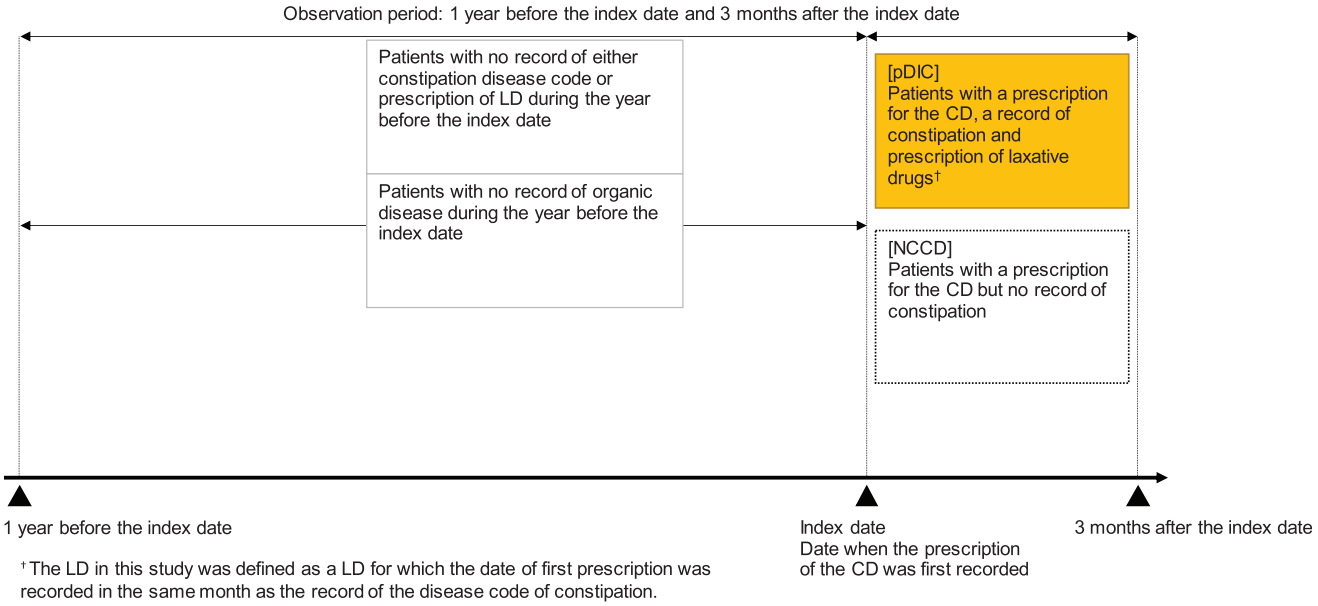

Figure 1 Study design. For both the constipation and the non-constipation cohorts, patients with organic diseases that can cause constipation (see Table S4) were excluded. CD; causative drug; LD; laxative drug; NCCD; non-constipation with CD; pDIC, potential drug-induced constipation.

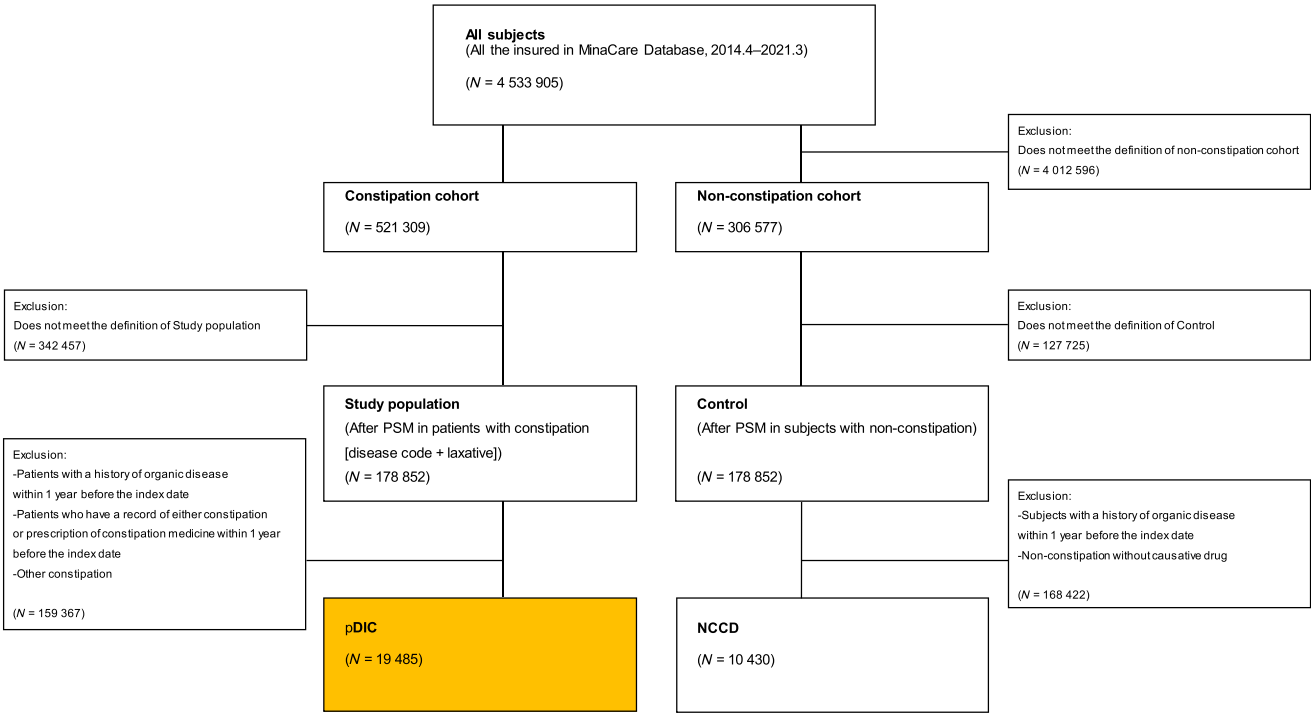

Figure 2 Patient flowchart. NCCD, non-constipation with causative drug; pDIC, potential drug-induced constipation; PSM, propensity score matching.

constipation cohorts. (ii) Subjects who were not considered to be diagnosed with DIC (Fig. 1), or had any record of a constipation disease code or a LD during the year before the index date were excluded from the constipation cohort.

The study population was classified based on whether or not the patient had any record of a CD prescription before the onset of constipation; the pDIC group included patients who had been prescribed a CD before constipation onset (Fig. 2). The control group was classified based on whether or not the patient had any record of a CD prescription; the non-constipation with CD (NCCD) group included patients who had been prescribed the CD (Fig. 2). The CDs were listed according to the WHO-ATC code with the corresponding Japanese drug code lists, and they were categorized based on the classification of drugs that can trigger DIC in the guidelines.[16] The LDs were also listed and categorized similarly.

The observation period was 1 year before the index date and 3 months after the index date. The health-checkup data closest to the index date, less than 1 year before or after the index date, was used.

Outcome measures. The primary outcome was the proportion of pDIC among all constipation patients who required therapeutic intervention in clinical practice.

The secondary outcomes included the following: (i) The period between the first prescription record of the CD and the recorded constipation diagnosis in the pDIC group, (ii) the number of patients who were prescribed a CD by drug class, (iii) the proportion for each category of laxatives prescribed, and (iv) evaluation of the following factors for their association with the occurrence of pDIC as explanatory variables, using the NCCD group as a reference: (i) each drug class that can cause DIC, (ii) gender, (iii) age, (iv) comorbidities (selected based on the Japanese guidelines;[16] Table S5), (v) health-checkup data (measurement items and lifestyle habits; Table S6).

Statistical analysis. Descriptive statistics of the data collected for each group were presented as the number of cases (%), mean (SD), and median (interquartile range). The significance level was set at 0.05, and the confidence interval (CI) was set at 95%.

Propensity score matching (PSM) was performed to adjust for differences in background characteristics between the study population and the control group. Propensity scores were calculated, and a 1:1 PSM (nonreciprocal sampling, nearest neighbor matching, caliper of 0.20) was performed using the study population and control group as objective variables, and age at the index date, sex, and the year of the index date as explanatory variables. The primary outcome was calculated by dividing the number of subjects in the pDIC group by the number of subjects in the study population. As for the secondary outcomes, the following were calculated for the pDIC group: (i) The period between the first prescription of the CD and the recorded constipation diagnosis was calculated in days from the index date to the day the constipation disease name was first recorded. (ii) The number and proportion of each CD class were calculated as of the index date. (iii) The LD with a first prescription date recorded in the same month as the constipation diagnosis record was used

for the outcome measurement. The number and proportion of prescriptions of the LDs by drug class within 3 months after the index date were calculated. (iv) To identify the factors that may influence the occurrence of constipation after a CD prescription, univariate logistic regression analysis was performed with the occurrence of constipation as the objective variable and the factors associated with treated constipation mentioned in the previous outcome measure section as explanatory variables for the pDIC group and NCCD group. The parameter estimates and their standard errors, *P* values, odds ratios, and 95% CI were calculated. Based on the results of univariate logistic regression analysis, candidate factors were selected using a stepwise variable selection method, and multivariate logistic regression analysis was performed with the occurrence of constipation as the objective variable and the candidate factors as the explanatory variables. The significance level for adding or removing each variable from the model was set at 0.20.

All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. In the flowchart of the subjects of this study (Fig. 2), among all subjects, 521 309 patients (11.5%) had at least one recorded constipation disease code. The study population included 178 852 patients after PSM was performed. The non-constipation cohort included 306 577 subjects, after excluding 4 012 596 subjects who did not meet the criteria of the cohort. The control group consisted of 178 852 subjects after applying PSM. Among the study population, 19 485 patients met the criteria of the pDIC group. Among the control group, 10 430 subjects met the criteria of the NCCD group. The proportion of females was 50.8% and 65.4%, and the proportion of subjects over 65 years old was 17.5% and 10.8%, in the pDIC group and NCCD group, respectively (Table 1).

Table 1 Patient characteristics

	pDIC	NCCD
	n (%)	*n* (%)
Total	19 485	10 430
Sex		
Male	9584 (49.2)	3613 (34.6)
Female	9901 (50.8)	6817 (65.4)
Age (years)		
Mean (SD)	44.0 (20.3)	43.5 (18.9)
Median (Q1, Q3)	47 (32, 61)	47 (31, 74)
<65	16 071 (82.5)	9308 (89.2)
≥65	3414 (17.5)	1122 (10.8)
Comorbidity		
Psychiatric disorder	3555 (18.2)	2696 (25.8)
Endocrine-metabolic disease	3495 (17.9)	1910 (18.3)
Neurological disorder	922 (4.7)	238 (2.3)
Collagenosis	38 (0.2)	19 (0.2)
Amyloidosis	28 (0.1)	4 (0.0)
Drug classes that can cause DIC		
Cardiovascular drugs	9330 (47.9)	4827 (46.3)
Psychotropic drugs	7095 (36.4)	4207 (40.3)
Anticholinergics	3847 (19.7)	1621 (15.5)
Opioid analgesics	1785 (9.2)	268 (2.6)
Diuretics	677 (3.5)	256 (2.5)
Antiparkinsonian drugs	621 (3.2)	187 (1.8)
Iron supplement	340 (1.7)	86 (0.8)
Aluminum antacids	256 (1.3)	82 (0.8)
Adsorbent, anion exchange resin drugs	206 (1.1)	31 (0.3)
Antidiarrheals	199 (1.0)	63 (0.6)
Antiemetics	134 (0.7)	43 (0.4)
Chemotherapeutic drugs	31 (0.2)	3 (0.0)

DIC, drug-induced constipation; NCCD, non constipation with causative drug; pDIC, potential DIC; Q1, first quartile; Q3, third quartile.

Primary outcome. Among the study population, 10.9% (19 485/178 852 patients) met the criteria for the pDIC group (Fig. 3a).

Secondary outcomes. The median (Q1, Q3) period between the first recorded CD prescription and the first recorded constipation diagnosis was 38.0 days (28.0, 59.0) (Table S7).

In the pDIC group, the most recorded drug class was cardiovascular drugs (47.9%), followed by psychotropic drugs (36.4%) and anticholinergics (19.7%) in Table 1. A similar trend was observed in the NCCD group. In the prescribed LD class for the pDIC group, the most recorded prescribed LDs were osmotic laxatives (50.4%), followed by stimulant laxatives (32.7%) and probiotics (18.8%) in Figure 3b.

Univariate logistic regression analysis showed that 35 factors were associated with the occurrence of pDIC, including all CD classes, sex, age, comorbidities (neurological disorder, amyloidosis, and psychiatric disorder), health-checkup data (height, BMI, waist circumference, blood pressure, visceral fat area, and laboratory data), and lifestyle habits (smoking and bedtime snacks) (Table S8). In the CD classes, the odds ratio (95% CI) was the highest for chemotherapeutic drugs (5.51 [1.69, 18.01]), followed by opioid analgesics (3.82 [3.35, 4.36]) and adsorbent, anion exchange resin drugs (3.58 [2.45, 5.23]). As for comorbidities, the odds ratio was the highest for amyloidosis (3.75 [1.31, 10.69]), followed by neurological disorder (2.13 [1.84, 2.46]). For the lifestyle habits recorded, smoking history had the highest odds ratio (1.17 [1.08, 1.28]).

Multivariate logistic regression analysis showed significant differences in 16 factors, including all drug classes that can lead to DIC, being male, and comorbidities (endocrine-metabolic disease, neurological disorder, and amyloidosis), in Table 2. The odds ratio for the CD class was the highest for opioid analgesics (4.73 [4.13, 5.42]), followed by iron supplement (4.71 [3.67, 6.05]), and adsorbent, anion exchange resin drugs (4.49 [3.05, 6.62]). As for comorbidities, amyloidosis (3.03 [1.04, 8.87]) had the highest odds ratio, followed by neurological disorder (1.98 [1.67, 2.35]).

Discussion

To the best of our knowledge, this is the first report to investigate the current situation of DIC based on real-world data in Japan. Our findings suggest that DIC may account for approximately 11% of all treated constipation cases, indicating that it is relatively common in clinical practice. The median period between

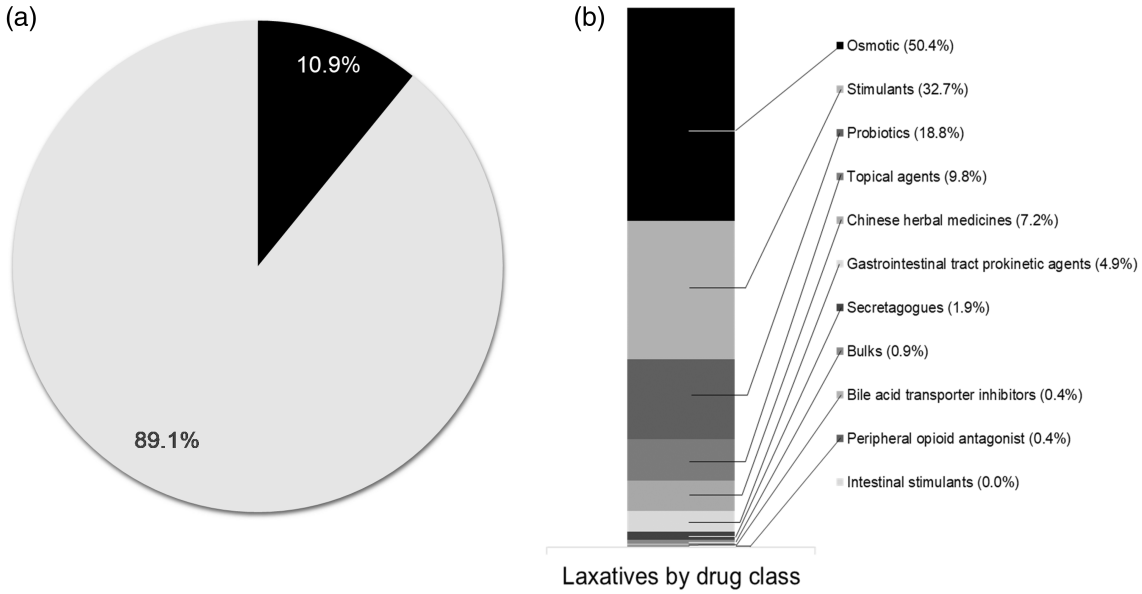

Figure 3 The proportion of potential drug-induced constipation (pDIC) and the prescribed medications for the treatment. (a) The proportion of pDIC among all treated constipation. ■, pDIC; ■, other constipation. (b) The relative frequency of laxatives prescribed for pDIC, categorized by drug class. The overall proportion of medications for constipation exceeded 100% because a single patient could be prescribed two or more laxatives at the same time.

Table 2 Factors associated with the occurrence of potential DIC (logistic regression analysis: multivariate[†])

Parameter	Level	Reference	Parameter estimate	Standard error	*P* value	Odds ratio	95% CI
Drug classes that can cause DIC							
Anticholinergics	Yes	No	0.348	0.022	<0.001	2.01	(1.84, 2.19)
Psychotropic drugs	Yes	No	0.146	0.019	<0.001	1.34	(1.24, 1.45)
Antiparkinsonian drugs	Yes	No	0.241	0.050	<0.001	1.62	(1.33, 1.97)
Opioid analgesics	Yes	No	0.777	0.035	<0.001	4.73	(4.13, 5.42)
Chemotherapeutic drugs	Yes	No	0.687	0.311	0.027	3.95	(1.17, 13.36)
Cardiovascular drugs	Yes	No	0.203	0.020	<0.001	1.50	(1.39, 1.62)
Diuretics	Yes	No	0.267	0.040	<0.001	1.71	(1.46, 1.99)
Aluminum antacids	Yes	No	0.485	0.067	<0.001	2.64	(2.03, 3.42)
Iron supplement	Yes	No	0.775	0.064	<0.001	4.71	(3.67, 6.05)
Adsorbent, anion exchange resin drugs	Yes	No	0.751	0.099	<0.001	4.49	(3.05, 6.62)
Antiemetics	Yes	No	0.324	0.093	<0.001	1.91	(1.33, 2.75)
Antidiarrheals	Yes	No	0.421	0.075	<0.001	2.32	(1.73, 3.12)
Sex	Female	Male	−0.307	0.013	<0.001	0.54	(0.51, 0.57)
Age			0.001	0.001	0.074	1.00	(1.00, 1.00)
Comorbidity							
Endocrine-metabolic disease	Yes	No	−0.078	0.017	<0.001	0.86	(0.80, 0.92)
Neurological disorder	Yes	No	0.342	0.043	<0.001	1.98	(1.67, 2.35)
Collagenosis	Yes	No	0.188	0.143	0.189	1.46	(0.83, 2.55)
Amyloidosis	Yes	No	0.554	0.274	0.043	3.03	(1.04, 8.87)

[†]Multivariate logistic regression analysis was performed using a stepwise variable selection method.
CI, confidence interval; DIC, drug-induced constipation; pDIC, potential DIC.

the first prescription of the CD and pDIC diagnosis was 38.0 days, which may reflect early complaints of constipation by patients, because prescriptions are typically given on a 30-day cycle, especially for chronic diseases in Japan.[20] However, it does not rule out that the patients or healthcare providers did not suspect the association between constipation and the prescribed CDs when constipation occurred after long-term use of the CDs. Considering that DIC may lead to poor adherence to the medication for the primary disease, physicians should be aware of the possibility of DIC when prescribing the CDs. The treatment strategy for DIC differs from other constipation treatments, and may require dose adjustments of the CDs and the

subsequent evidence-based pharmacotherapy. Therefore, when treating constipation, the first step should be to determine whether or not it is a DIC caused by prescription drugs, and evidence-based treatment should be considered in case the CD cannot be reduced or withdrawn.

Cardiovascular drugs, psychotropic drugs, and anticholinergics were the most frequently prescribed CD classes among those listed in the guidelines.[16] Since these drugs can be widely prescribed regardless of medical specialty in clinical practice, most cases of pDIC may be mistreated as FC by non-gastroenterologists.

Traditionally, osmotic laxatives or stimulant laxatives are used for treating chronic constipation in Japan, although other more beneficial drugs with novel mechanisms of action have been recently approved and are clinically available.[21] The use of LDs for pDIC observed in this study did not differ from the general treatment for FC, despite traditional therapies having little evidence for treating DIC. This may indicate that pDIC was not treated based on etiology. For instance, the peripheral opioid antagonist, naldemedine, the only approved drug indicated for OIC in Japan,[22] was prescribed for only 73 cases, despite that 1785 patients with constipation were prescribed opioid analgesics. Secretagogues were also rarely prescribed, even though there is evidence of lubiprostone for treating OIC. Taken together, this suggests a low awareness of OIC or DIC. Since very few reports investigated the efficacy and safety of medications for treating any type of DIC other than OIC, further research is needed to identify appropriate DIC treatment strategies that physicians could adopt based on etiology.

The multivariate analysis showed that all drug classes listed in the guidelines[16] as capable of causing DIC were significantly associated with the occurrence of pDIC, suggesting that the list is reasonable from a clinical perspective. In particular, the odds ratios were high for opioid analgesics (4.73), iron supplement (4.71), and adsorbent, anion exchange resin drugs (4.49), which was consistent with previous reports,[23–27] indicating the need to be especially cautious about DIC when prescribing these drugs. Males were found to be at a greater risk of developing pDIC in this study, although constipation is generally more common in females than males.[1,17–19] Although it is difficult to interpret this phenomenon with the limited amount of data, it may be associated with CDs, such as cardiovascular drugs, being prescribed more often for males than females. Further studies are needed to clarify how gender differences could influence the development of DIC. Regarding comorbidities, amyloidosis and neurological diseases were significantly associated with DIC, which was consistent with previous studies that associated amyloidosis[28] or Parkinson's disease[29] with constipation. These symptomatic constipation cases may overlap with pDIC. Therefore, it may be necessary to consider not only DIC but also symptomatic constipation, especially in patients with these underlying diseases.

This study has several limitations. First, the MinaCare database used in this study consists of company employees and their dependents who were enrolled in a health insurance association for private companies. Therefore, it may not adequately represent the general population of Japan. In particular, this database lacks coverage for the elderly over the age of 75. However, previous studies have shown that the results obtained from MinaCare data are consistent with those from national data sources.[30] Furthermore, the MinaCare database does not include workers in primary industries such as agriculture, fisheries, and forestry, limiting the generalizability of the study population to the general Japanese population in terms of employment type and geography. Thus, the regions where primary industries dominate were underrepresented in the study population. Second, the MinaCare database defines constipation by ICD-10 codes and disease codes, which may differ from the actual diagnosis if the disease codes had been entered for insurance claims or medical purposes. Furthermore, constipation defined by disease codes may include organic and symptomatic constipation, resulting in an overestimation of DIC. Third, many insured individuals did not have health-checkup data at the index date (the date when the first prescription of the CD was recorded). Thus, we used health-checkup data less than 1 year before or after the index date, which would best reflect the health status of the insured individuals at the index date. Therefore, post-index date data may have been employed, and a factorial search for "constipation with treatment" was conducted using information that was not available at the index date. Additionally, a significant proportion of data was missing in the lifestyle habits section, but the proportion of participants with missing data was similar in the two groups compared. Fourth, the drug information in this study was analyzed using prescription data, which may not accurately reflect actual drug use. Since the analysis in this study is limited to the CDs defined in the guidelines,[16] other potential CDs were not considered. Furthermore, the impact of an individual drug and duplicate use of different drugs were not investigated. Fifth, the study did not calculate the average number of potential CDs and the cumulative number of prescribed CDs for either the pDIC group or the NCCD group. If a patient had a high number of potential CD or prescribed CD for constipation, possible effects due to the accumulation of those CDs were not considered.

Conclusions

This study showed that pDIC may account for approximately 11% of all treated constipation cases. The factors associated with pDIC included all drug classes ever considered to cause DIC, male gender, and comorbidities, such as amyloidosis and neurological diseases. Given that DIC requires a different treatment strategy than other types of constipation, including dose adjustments of the CD to improve compliance with therapy, it should be widely noted by physicians in clinical practice to provide patients with optimized treatment regimens based on the etiology of constipation.

Acknowledgments

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Ethics approval statement

The database used in this study contains only anonymized data and does not include personal information. Therefore, the research using this unlinkable anonymized data was approved by

the Ethics Committee of the nonprofit organization MINS (approval number: 220220, approval date: December 22, 2022) in accordance with the Japanese government's "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects." As the data were anonymized, obtaining patient consent was not required.

Data availability statement. The MinaCare data are proprietary to MinaCare, Co., Ltd. and are not publicly available for research purposes. Researchers who wish to access the data for research purposes should contact MinaCare Co., Ltd. (mc_info@minacare.co.jp) to establish a data use agreement and pay a data availability fee.

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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. List of codes for identification of constipation.
Table S2. List of codes for identification of laxative drugs.
Table S3. List of codes for identification of causative drugs.
Table S4. List of codes for identification of organic diseases.
Table S5. List of codes for identification of comorbidities.
Table S6. Patient characteristics summary (health-checkup data).
Table S7. Period between the first recorded causative drug prescription and treated constipation.
Table S8. Factors associated with the occurence of potential drug-induced constipation (logistic regression analysis: univariate).