Original research

Risk of drug-induced interstitial lung disease in hospitalised patients: a nested case–control study

Taisuke Jo,[1,2] Nobuaki Michihata,[2] Hayato Yamana,[2] Kojiro Morita,[3,4] Miho Ishimaru,[3,4] Yasuhiro Yamauchi,[1] Wakae Hasegawa,[1] Hirokazu Urushiyama,[1] Kazuaki Uda,[4] Hiroki Matsui,[4] Kiyohide Fushimi,[5] Hideo Yasunaga,[4] Takahide Nagase[1]

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[1]Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Health Services Research, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[3]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[4]Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, Tokyo, Japan
[5]Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

Correspondence to
Dr Taisuke Jo, Department of Respiratory Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; jo-taisuke@umin.ac.jp

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ABSTRACT

Introduction Information on drug-induced interstitial lung disease (DILD) is limited due to its low incidence. This study investigated the frequencies of drug categories with potential risk in patients developing DILD during hospitalisation and analysed the risk of developing DILD associated with each of these drugs.

Methods Using a Japanese national inpatient database, we identified patients without interstitial pneumonia on admission who developed DILD and required corticosteroid therapy during hospitalisation from July 2010 to March 2016. We conducted a nested case–control study; four controls from the entire non-DILD patient cohort were matched to each DILD case on age, sex, main diagnosis, admission year and hospital. We defined 42 classified categories of drugs with 216 generic names as drugs with potential risk of DILD, and we identified the use of these drugs during hospitalisation for each patient. We analysed the association between each drug category and DILD development using conditional logistic regression analyses.

Results We retrospectively identified 2342 patients who developed DILD. After one-to-four case–control matching, 1541 case patients were matched with 5677 control patients. Six drug categories were significantly associated with the increased occurrence of DILD. These included epidermal growth factor receptor inhibitors (OR: 16.84, 95% CI 9.32 to 30.41) and class III antiarrhythmic drugs (OR: 7.01, 95% CI 3.86 to 12.73). Statins were associated with reduced risk of DILD (OR: 0.68, 95% CI 0.50 to 0.92).

Conclusions We demonstrated significant associations between various drug categories and DILD. Our findings provide useful information on drug categories with potential risk to help physicians prevent and treat DILD.

Key messages

What is the key question?
► Which drugs were associated with a higher risk of drug-induced interstitial lung disease?

What is the bottom line?
► Among the drugs with potential risk of drug-induced interstitial lung disease, epidermal growth factor receptor inhibitors and class III antiarrhythmic drugs are highly likely to lead to the development of drug-induced interstitial lung disease.

Why read on?
► This study is the first to evaluate the risk of developing drug-induced interstitial lung disease associated with multiple drugs with potential risk.

INTRODUCTION

Lung injury is an increasingly common cause of morbidity and mortality in patients treated with either cytotoxic or non-cytotoxic drugs. Studies have reported various drugs that potentially cause drug-induced interstitial lung disease (DILD), including chemotherapeutic agents, antibiotics, antiarrhythmic agents and immunosuppressants.[1–6] Corticosteroids are used for treating lung injury following DILD.[1–11]

Identifying a specific drug with potential risk for each patient who develops DILD is challenging due to the rarity of the disease. Although many studies have presented case report and case series data, these findings cannot clarify causal relationships between drugs and interstitial lung disease (ILD) due to the lack of a control group. One previous cohort study reported drugs associated with acute lung injury,[6] but the generalisability of that study's results may be limited due to the small sample size. Difficulties in identifying drugs with potential risk of DILD may also be attributed to the ineffectiveness of laboratory testing, including drug lymphocyte stimulation test.[12 13]

The present study aimed to measure the frequencies of drug categories with potential risk of DILD among patients who developed DILD during hospitalisation and to conduct a nested case–control study to evaluate the risk of developing DILD associated with each drug, using a Japanese national inpatient database.

MATERIALS AND METHODS

Data collection

We obtained data from the Diagnosis Procedure Combination Database, which is a nationwide inpatient database in Japan. Data on discharge abstracts and administrative claims are collected from approximately seven million inpatients per year in around 1200 hospitals throughout Japan. The database includes main diagnoses, primary diagnosis on admission, comorbidities on admission and complications during hospitalisation, all of which

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are recorded by attending physicians using International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. The database also contains detailed information on age, sex, body mass index, activities of daily living, smoking status, medication, interventional procedures, surgical procedures and discharge status including in-hospital mortality.

Identification of cases

We conducted a nested case–control study. In the first step, we identified inpatients who developed DILD after admission from 1 July 2010 to 31 March 2016. We excluded patients who were diagnosed with DILD or ILD on admission. DILD was defined using the following ICD-10 codes: J702 (acute drug-induced interstitial lung disorders), J703 (chronic drug-induced interstitial lung disorders) and J704 (drug-induced interstitial lung disorders, unspecified). ILD was defined using the following ICD-10 codes: B221 (HIV interstitial pneumonia), J700 (radiation pneumonitis), J701 (chronic and other pulmonary symptoms due to radiation), J841 (other ILDs with pulmonary fibrosis), J848 (other specified ILDs), J849 (ILD, unspecified), J990 (rheumatoid lung disease), J991 (respiratory disorders in other diffuse connective tissue disorders), M051 (rheumatoid lung disease), M313 (Wegener's granulomatosis), M321 (systemic lupus erythematosus with complications in organs or organ systems), M330 (juvenile dermatomyositis), M331 (other dermatomyositis), M332 (polymyositis) and M351 (other overlapping syndromes). Because corticosteroids are used to treat lung injury following DILD,[1–11] we used the initiation of systemic corticosteroid therapy for treating lung injury following DILD as a proxy measure for the onset of DILD. Therefore, only patients with DILD who required corticosteroid therapy were selected as case patients in this study. Systemic corticosteroid therapy for treating lung injury following DILD was defined as follows: (1) high-dose corticosteroid therapy (>500 mg of prednisolone per day for ≥3 days); (2) medium-dose corticosteroid therapy (201–500 mg of prednisolone per day for ≥3 days); and (3) low-dose corticosteroid therapy (30–200 mg of prednisolone per day for ≥7 days). We evaluated the prescription duration of systemic corticosteroids for the case and control patients.

Case–control matching

From the entire cohort during the study period, four controls were matched to each case, using risk-set sampling with replacement. More specifically, for each patient with DILD, we selected four control patients with the same primary diagnosis (assessed using the first three digits of the patient's ICD-10 codes on admission), sex and age (within a 10-year difference) who were also hospitalised in the same hospital in the same fiscal year or consecutive fiscal years. In the risk-set sampling, control patients were selected from patients whose length of stay was longer than the duration from admission to the initiation of corticosteroid therapy in the corresponding case patients. Control patients were also selected from patients with DILD who received corticosteroid therapy initiated later than this therapy was initiated for the corresponding case patients. We excluded case patients for whom no matched control patient was found. When more than four control patients were eligible to be matched to a case patient, we randomly selected four control patients. We omitted case–control patient groups when case patients had corticosteroid therapy initiated on the day of admission.

Definition of covariates

Based on Quan *et al*'s[14] algorithm, ICD-10 codes for comorbidities were converted to a score, and the sum of these scores was used to calculate the Charlson Comorbidity Index. We assessed the existence of a cancer diagnosis, including lung cancer (ICD-10 code: C34) and other cancers. Activities of daily living on admission were examined using the Barthel index (0–100).[15] We categorised the Barthel index as 0–90 or 95–100. The Brinkman index was calculated as the number of cigarettes smoked per day multiplied by the number of years the patient smoked. We categorised the Brinkman index as <200, 200–599 or ≥600. Body mass index was categorised into the following three groups: <18.5, 18.5–24.9 or ≥25.0 kg/m^2. All missing values on categorical variables were categorised as missing. We evaluated the severity of patients at hospitalisation by assessing whether they were admitted to an intensive care unit within 2 days of hospitalisation or received mechanical ventilation within 2 days of hospitalisation.

Definition and classification of drugs with potential risk

We identified drugs that were potentially related to DILD using the information provided in the product package insert from the Pharmaceuticals and Medical Devices Agency (http://www.pmda.go.jp/PmdaSearch/iyakuSearch/), which reported 323 generic names and 5726 trade names of drugs that may cause interstitial pneumonia as an adverse drug reaction. We classified the identified drugs into 75 categories on the basis of their function and mechanism of action. Of these categories, we omitted 33 in which none of the drugs was referred to in any of the five review articles on DILD, including a recent systematic review,[1–5] or population-based cohort study.[6] We thus evaluated 42 drug categories with 216 generic names that are generally accepted as drugs with potential risk of DILD (online supplemental e-Table 1).

We examined the use of these drugs among all case and control patients. The number of drug categories with potential risk prescribed for each patient was also assessed. Corticosteroids prescribed before drugs with potential risk may have modulated the clinical course of patients with potential to develop DILD. Thus, when any of the candidate drugs in these drug categories were prescribed to a patient after prescription of systemic corticosteroids, regardless of the prescribed dose and duration, these drugs were not regarded as candidates for drugs with potential risk of DILD. Furthermore, drugs that were prescribed within 3 days before discharge for patients who were discharged alive were not considered drugs with potential risk.

Statistical analysis

The demographic characteristics of the patients are expressed as numbers and percentages. Standardised mean difference was used to evaluate the balance of background characteristics between the case and control patients[16] and an absolute value of <0.1 was considered well balanced. ORs and 95% CIs of each drug category were calculated using a univariate conditional logistic regression model. We selected drug categories that were significantly associated with DILD in the univariate analyses. We then performed a multivariable conditional logistic regression analysis with selected drug categories. We also included the Barthel index, Brinkman index, body mass index, Charlson Comorbidity Index, presence of lung cancer, presence of other cancer, intensive care unit admission within 2 days of hospitalisation and mechanical ventilation within 2 days of hospitalisation as independent variables in the model. Because the Barthel

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index, Brinkman index and body mass index had missing values, we performed multiple imputation for conditional multivariable logistic regression analysis. In brief, we used in-hospital mortality, age, sex, fiscal year, length of stay, diagnosis of lung cancer, diagnosis of malignancy other than lung cancer, intensive care unit admission during hospitalisation, mechanical ventilation during hospitalisation and all drug categories used for ≥5 patients (online supplemental e-Table 2) for multivariate imputation by chained equation, and 20 imputed data sets were obtained. These data sets were then combined using Rubin's rule to acquire combined imputation estimates and SEs.[17]

A p value <0.05 was considered significant. Statistical analyses were performed using SPSS V.25.0 and Stata V.14.

RESULTS

We identified 2342 cases who developed DILD requiring corticosteroid therapy during hospitalisation in the study period. Four control patients were matched to each case patient from a total of 41 771 128 non-case hospitalised patients (online supplemental e-Figure 1). Of the cases, we excluded 292 that were not matched to any control patients. There were 118 cases that could be matched with only 1 control patient, 102 cases that could be matched with only 2 control patients, and 83 cases that could be matched with only 3 control patients.

We ultimately enrolled a total of 7218 patients, including 1541 cases and 5677 controls. Among the case patients, 1246 (81%), 119 (7.7%) and 671 (44%) received high-dose, moderate-dose and low-dose corticosteroid therapy, respectively. The median ages of the case and control patients were 73 (IQR: 66–78) years and 73 (IQR: 66–79) years, respectively. Male patients made up 70% of both the case and the control group. The median length of hospital stay was 37 (25–57) days for case patients and 20 (12–36) days for control patients. The median prescription duration of systemic corticosteroids was 29 (17–46) days for case patients and 9 (3–26) days for control patients. The number (%) of in-hospital deaths among the case and control patients was 535 (35%) and 610 (11%), respectively.

The characteristics, comorbidities, treatments at hospitalisation and number of prescribed drugs with potential risk of DILD of the case and control patients are shown in table 1. Matched variables (age, sex and fiscal year) were well balanced between the cases and controls, except for fiscal years 2014 and 2015, which had standardised mean differences of 0.112 and 0.100, respectively. The percentages of case and control patients requiring imputation due to missing data for activities of daily living, Brinkman index and body mass index were 13.8% and 11.9%, 10.5% and 9.7%, and 5.0% and 6.1%, respectively.

One or more of the drug categories with potential risk were prescribed for 56% of the case patients and 45% of the control patients. The number of patients who received agents with potential risk, including all drugs prescribed during hospitalisation and those prescribed before prescription of any corticosteroids, is presented in online supplemental e-Table 2. We excluded a total of 23 drug categories because small numbers of patients (<5) were administered these types of drugs in either the case group or the control group (online supplemental e-Figure 2).

Approximately 6.8% of the control patients received corticosteroids equivalent to one or more instances of high-dose, medium-dose or low-dose corticosteroid therapy. Table 2 shows the results of the univariate conditional logistic regression analyses for treatment with systemic corticosteroids and in-hospital death. The percentage of patients treated with systemic corticosteroids was larger for case patients than for control patients, particularly for high-dose corticosteroid therapy (80.9% vs 2.8%). Case patients had higher in-hospital mortality than did control patients (OR: 5.2, 95% CI 4.49 to 6.10).

The number of patients who received agents with potential risk eligible for further analysis (ie, those that were not prescribed during the last 3 days of hospitalisation) and the results of the univariate conditional logistic regression analyses for the occurrence of DILD are shown in table 3. Of the 17 drug categories, 10 showed significant differences in the occurrence of DILD between cases and controls.

Table 4 shows the results of the multivariable conditional logistic regression analysis with multiple imputation including 10 drug categories. Higher Charlson Comorbidity Index, higher Brinkman index and lower body mass index were associated with an increased risk of developing DILD. Activities of daily living score was not significantly associated with the occurrence of DILD. Patients with lung cancer or other cancer had a higher incidence of DILD. Intensive care unit admission within 2 days of hospitalisation was not associated with an increased incidence of DILD, whereas patients who were mechanically ventilated within 2 days of hospitalisation had an increased incidence of DILD. Of the 10 drug categories, 6 were significantly associated with the development of DILD, including class III antiarrhythmic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), sulfamethoxazole/trimethoprim, quinolones, beta-lactams and epidermal growth factor receptor (EGFR) inhibitors. The drug categories with OR >5 included EGFR inhibitors (OR: 16.84, 95% CI 9.32 to 30.41) and class III antiarrhythmic drugs (OR: 7.01, 95% CI 3.86 to 12.73). The drug categories with OR of 2–5 included sulfamethoxazole/trimethoprim and quinolones. Statins were the only drug category with an OR <1, and this association was statistically significant.

DISCUSSION

The present nested case–control study using a nationwide inpatient database investigated the use of 42 drug categories with potential risk in cases that developed DILD during hospitalisation and matched controls, finding significant associations between 6 drug categories and the occurrence of DILD.

We evaluated only drugs that were mentioned in previous review articles on DILD,[1–6] and we used drug categories with similar biological activity for two reasons: (1) Evaluating each drug individually would increase the number of variables for drugs with potential risk, and each drug would have fewer patients to whom it was prescribed, potentially reducing statistical power. (2) Because some candidate drugs were domestic drugs, we used drug categories to avoid eliminating drugs due to the absence of previous reports in English. Nevertheless, we may still have missed some significant associations by eliminating drugs due to the absence of previous reports. However, the evaluated drugs can be considered core drugs for DILD because they are likely to be drugs with relatively high risk of developing DILD or with risk of developing severe DILD.

Previous studies have identified male sex, older age and pre-existing lung disease as common risk factors of DILD caused by amiodarone, methotrexate and EGFR inhibitor.[18–22] In line with these previous studies, in our study, DILD was more frequent in male patients and 88% of patients with DILD were aged ≥60 years. Because multiple comorbidities may be a source of confounding (ie, patients with multiple comorbidities are likely to be exposed to multiple treatments, including drugs with potential risk, and may also be vulnerable to adverse events), we included the Charlson Comorbidity Index in our multivariable regression model. We also found

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Table 1 Patient characteristics of the matched case and control groups

Characteristics	Cases (n=1541)		Controls (n=5677)		SMD
	n	%	n	%	
Age, years					
≤10	0	0.0	0	0.0	0.005
11–20	1	0.1	3	0.1	−0.003
21–30	2	0.1	8	0.1	0.017
31–40	8	0.5	23	0.4	0.048
41–50	38	2.5	101	1.8	0.024
51–60	137	8.9	467	8.2	−0.027
61–70	447	29.0	1717	30.2	0.061
71–80	647	42.0	2215	39.7	−0.073
81–90	248	16.1	1071	18.9	−0.042
≥91	15	0.8	72	1.3	
Sex					0.010
Male	1079	70.0	4000	70.5	
Female	462	30.0	1677	29.5	
Fiscal year					
2010	92	6.0	330	5.8	0.009
2011	183	11.9	701	12.3	−0.014
2012	293	19.0	1069	18.8	0.005
2013	312	20.3	1087	19.2	0.028
2014	307	19.9	1420	25.0	0.112
2015	353	22.9	1070	18.9	0.100
Activities of daily living (Barthel index)					
95–100	819	53.1	3051	53.7	−0.012
0–90	509	33.0	1951	34.4	−0.028
Missing	213	13.8	675	11.9	0.058
Brinkman index					
0–199	712	46.2	3606	63.5	−0.353
200–599	164	10.6	483	8.5	0.073
≥600	504	32.7	1036	18.3	0.336
Missing	161	10.5	552	9.7	0.024
Body mass index, kg/m^2					
<18.50	247	16.0	1233	21.7	−0.146
18.50–24.99	1005	65.2	3132	55.2	0.206
≥25.00	212	13.8	964	17.0	−0.089
Missing	77	5.0	348	6.1	−0.049
Charlson Comorbidity Index					
0–2	983	63.8	4312	76.0	−0.268
3–5	105	6.8	356	6.3	0.022
≥6	453	29.4	1009	17.8	0.278
Cancer					
Lung cancer	555	36.0	1725	30.4	0.120
Other cancer	481	31.2	1514	26.7	0.100
ICU admission within 2 days of hospitalisation	55	3.6	261	4.6	−0.052
Mechanical ventilation within 2 days of hospitalisation	74	4.8	219	3.9	0.046

ICU, intensive care unit; SMD, standardised mean difference.

that having a lower body mass index and having a higher Charlson Comorbidity Index score were significant independent risk factors for the development of DILD. A previous study reported that lung cancer was a strong predictor of ILD associated with gemcitabine.[23] In line with this previous study, lung cancer was found to be a significant risk factor for DILD in our study.

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Table 2 Comparison of systemic corticosteroid treatments and in-hospital death between case and control patients using univariate conditional logistic regression analyses

	Cases (n=1541)		Controls (n=5677)				
Drug category with potential risk	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**P value***
High-dose corticosteroid therapy	1246	80.9	156	2.8	185.92	123.0 to 280.9	<0.001
Moderate-dose corticosteroid therapy	119	7.7	28	0.5	19.30	12.10 to 30.80	<0.001
Low-dose corticosteroid therapy	671	43.5	263	4.6	18.47	15.17 to 22.48	<0.001
Outcome of DILD							
In-hospital death	535	34.7	610	10.8	5.24	4.49 to 6.10	<0.001

*Denotes p values derived from univariate conditional logistic regression.
DILD, drug-induced interstitial lung disease.

To the best of our knowledge, no previous large-scale study has shown the differences in risk among drugs that are likely to be responsible for DILD. Drugs with potential risk were prescribed for 56% of the cases. Presumably, in the other 44% of the cases, either DILD was caused by drugs that were not included in our study or delayed-onset DILD caused by drugs with potential risk prescribed in outpatient settings developed during hospitalisation. The lack of data in outpatient settings may also limit the applicability of our findings because hospitalised patients are generally sicker and may have higher risk of development of DILD, compared with outpatients. Nevertheless, our study showed that EGFR inhibitors and class III antiarrhythmic drugs were highly likely to lead to the development of DILD (OR ≥5).

Our results support the findings of previous small cohort studies and case reports. EGFR showed the highest OR among all drug categories included in this study. A previous cohort study reported that the risk of developing DILD among patients with lung cancer was generally higher in patients taking gefitinib than in patients receiving cytotoxic chemotherapy, particularly in the first 4 weeks.[21] A class III antiarrhythmic drug (amiodarone) was found to be associated with acute lung injury in a recent retrospective cohort study.[6] However, to date, no large cohort study has explored the effects of these drugs.

Our findings also support the results of previous reports that have suggested a potential risk of interstitial pneumonia in patients receiving a quinolone,[2 24–26] which is thought to potentially be associated with the risk of developing DILD.

Although cases of DILD caused by NSAIDs[2 27] and beta-lactams[2 5 28] have previously been reported and these drugs were significantly associated with increased incidence of DILD in our study, the ORs of these drug categories were <2. Despite the statistical significance of these associations, the clinical impact of drugs with relatively low ORs may be limited. However, because these drugs are commonly prescribed and the key to the successful treatment of DILD is early recognition of drugs with potential risk, care should be taken when using these drugs in patients who develop DILD.

Table 3 Drug categories with potential risk of drug-induced interstitial lung disease prescribed before corticosteroids and ≤3 days before discharge during hospitalisation and the results of univariate conditional logistic regression analyses for the occurrence of drug-induced interstitial lung disease

	Cases (n=1541)		Controls (n=5677)				
Drug category with potential risk	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**P value**
Antiplatelets	44	2.9	150	2.6	1.01	0.69 to 1.46	0.977
Anticoagulants	7	0.5	9	0.2	3.11	1.16 to 8.35	0.024
Statins	60	3.9	294	5.2	0.68	0.50 to 0.92	0.012
Sodium channel blockers	10	0.6	30	0.5	1.28	0.61 to 2.67	0.511
Class III antiarrhythmic drugs	45	2.9	35	0.6	6.80	3.96 to 11.66	<0.001
ACE inhibitor	9	0.6	18	0.3	1.83	0.80 to 4.20	0.156
Thiazides	11	0.7	67	1.2	0.59	0.31 to 1.14	0.116
NSAIDs	302	19.6	566	10.0	2.43	2.04 to 2.88	<0.001
Antiepileptics	16	1.0	53	0.9	1.07	0.59 to 1.94	0.836
Sulfamethoxazole/trimethoprim	14	0.9	17	0.3	2.89	1.36 to 6.13	0.006
Quinolones	175	11.4	246	4.3	2.93	2.35 to 3.65	<0.001
Tetracyclines	40	2.6	69	1.2	2.30	1.50 to 3.52	<0.001
Beta-lactams	639	41.5	1940	34.2	1.62	1.39 to 1.89	<0.001
Anti-TB drugs	14	0.9	28	0.5	2.14	0.94 to 4.89	0.071
EGFR inhibitors	73	4.7	22	0.4	16.48	9.57 to 28.39	<0.001
Pyrimidine	16	1.0	50	0.9	1.18	0.63 to 2.21	0.599
Anthracyclines	9	0.6	12	0.2	3.09	1.24 to 7.70	0.015

EGFR, epidermal growth factor receptor; NSAIDs, non-steroidal anti-inflammatory drugs.

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Table 4 Multivariable conditional logistic regression analysis for the occurrence of drug-induced interstitial lung disease

Characteristics	OR	95% CI	P value
Barthel index			
95–100	Reference		
0–90	0.93	0.78 to 1.09	0.352
Brinkman index			
0–199	Reference		
200–599	1.64	1.31 to 2.05	<0.001
≥600	2.54	2.17 to 2.98	<0.001
Body mass index			
<18.50	1.65	1.38 to 1.96	<0.001
18.50–24.99	Reference		
≥25.00	1.18	0.93 to 1.48	0.169
Charlson Comorbidity Index			
0–2	Reference		
3–5	1.01	0.77 to 1.32	0.955
≥6	2.39	2.00 to 2.86	<0.001
Lung cancer	2.38	1.81 to 3.12	<0.001
Other cancer (other than lung cancer)	1.77	1.43 to 2.20	<0.001
ICU admission within 2 days of hospitalisation	0.68	0.46 to 1.02	0.063
Mechanical ventilation within 2 days of hospitalisation	1.77	1.22 to 2.47	0.002
Drug category with potential risk			
Anticoagulants	2.58	0.76 to 8.81	0.130
Statins	0.53	0.37 to 0.75	<0.001
Class III antiarrhythmic drugs	7.01	3.86 to 12.73	<0.001
NSAIDs	1.90	1.56 to 2.31	<0.001
Sulfamethoxazole/trimethoprim	2.54	1.04 to 6.24	0.042
Quinolones	3.10	2.41 to 3.99	<0.001
Tetracyclines	1.60	0.97 to 2.66	0.067
Beta-lactams	1.54	1.29 to 1.84	<0.001
EGFR inhibitors	16.84	9.32 to 30.41	<0.001
Anthracyclines	1.89	0.68 to 5.23	0.223

Drug categories with potential risk of drug-induced interstitial lung disease with significant associations in the univariate analysis were included.
EGFR, epidermal growth factor receptor; ICU, intensive care unit; NSAIDs, non-steroidal anti-inflammatory drugs.

The only drug category with an OR <1 in this study was statins. Statin-induced pneumonitis is well recognised,[1–3 29 30] and the protective effect of statins in cases of lung disease, such as in acute lung injury,[31] radiation pneumonitis[32] and interstitial pneumonia,[33] has been discussed with mixed results. Two large-scale, nested case–control studies using insurance claims databases specifically evaluated the association between statins and ILD. A study conducted in Quebec found no association between the development of ILD and statins,[34] whereas a study in Japan reported a significant association between ILD and atorvastatin.[35] Our study has three potential advantages over these two studies. First, our study included only patients who were diagnosed during hospitalisation and were treated with corticosteroids; therefore, our study may have included patients with DILD with higher specificity and severity. Second, we assessed the discontinuation of drugs with potential risk; therefore, the drugs assessed in our study are more likely to be a risk. Third, in our study, risk factors were adjusted for various drugs with potential risk, allowing us to evaluate the independent risk of each drug category for patients using multiple drugs with potential risk. The exclusion of patients with mild DILD who recovered without the use of systemic corticosteroids may have biased our results. However, there is no evidence that DILD caused by statins is generally milder than DILD caused by other drugs. We speculate that statins are associated with only a modest risk of developing DILD requiring corticosteroid therapy, relative to the risk of other drugs prescribed during hospitalisation. Further studies are required to confirm our results.

The present study also did not find significant associations between many drug categories and DILD. However, this finding should be interpreted carefully, and we cannot conclude these drugs are safe because previous studies have suggested that most of these drug categories were potential risks. These drugs may have caused DILD in patients who recovered after discontinuing use of the drugs, and thus the risks associated with these drugs were not accurately evaluated in this study. In addition, the lack of significant findings in our study may simply reflect insufficient statistical power for infrequently used drugs.

The pre-existence of ILD and prior or concurrent use of corticosteroids may have been candidates for effect modifiers if they had been included in our study. We excluded patients who were diagnosed with ILD on admission for two reasons. First, ILD may also be a confounder due to its association with certain drugs evaluated in this study. For example, ILD is likely to be associated with both the use of EGFR inhibitors and the outcome. Second, distinguishing the development of DILD from the acute exacerbation of ILD may be difficult. Drugs used after systemic corticosteroids were excluded from the list of drugs with potential risk in this study. Corticosteroids are used for the treatment of severe DILD and therefore might modify the effects of exposure to the evaluated drugs on risk of DILD. Although we did not explore potential effect modifiers or interactions between drugs with potential risk of DILD in this study, our study will help foster future investigation.

The limitations of this study should be acknowledged. First, from the information in the database, we were unable to identify the exact date of the onset of DILD during hospitalisation. Thus, we were not able to definitely confirm that the drugs were used before the onset of DILD. We used the date of systemic corticosteroid treatment as a proxy for the date of the development of DILD. We were therefore unable to evaluate mild DILD from which patients recovered after discontinuing drugs, without systemic corticosteroid therapy. Second, in this study setting, we were unable to assess drugs such as cisplatin, which are coadministered with corticosteroids to prevent adverse effects. Third, we did not explore statistical interactions between the drugs. Fourth, several types of clinical data were not available in the database, including results of chest X-rays, high-resolution CT, pathology and blood testing. Severity, pathological manifestation and radiological phenotype of DILD could not be assessed. Fifth, we could not evaluate drug categories prescribed for a very small number of patients. Finally, this study was prone to confounding by indication because this was a retrospective database study.

In conclusion, we conducted a nested case–control study to identify significant associations between several drug categories and the occurrence of DILD in hospitalised patients who required corticosteroid therapy, using a national inpatient database. Our findings may provide useful information on drugs with potential risk of DILD, assisting physicians in the prevention and treatment of DILD.

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Contributors TJ: conception and design, data analysis and interpretation, and manuscript writing. NM, HYam, YY, WH, UH: conception and design, data analysis and interpretation, and final approval of the manuscript. KM, MI, KU, KF, HM: data collection, data analysis and final approval of the manuscript. HYas: conception and design, data collection, data analysis and interpretation, and manuscript writing. TN: conception and design and final approval of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The present study was approved by the Institutional Review Board of The University of Tokyo, which waived the requirement for patient informed consent due to the anonymous nature of the data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data cannot be made publicly available for ethical reasons as the data are patient data. Data are available to interested researchers upon reasonable request to the corresponding author, pending ethical approval.

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e-Table 1. Drug classification

Category Name	Generic Name
Antiplatelets	clopidogrel, cilostazol, ticlopidine[2], beraprost, beraprost–long acting, complavin
Anticoagulants [2,3]	dabigatran
Statins[1,2,3]	atorvastatin[2], simvastatin, pitavastatin, fluvastatin, pravastatin, rosuvastatin, amlodipine/atorvastatin
Sodium channel blockers[4,5†]	mexiletine, aprindine, cibenzoline
Beta blocker	acebutolol[2]
Class III antiarrhythmic drugs	amiodarone[1–6]
Calcium channel blockers	bepridil[1], amlodipine/atorvastatin, telmisartan/amlodipine, valsartan/amlodipine, valsartan/cilnidipine, candesartan/amlodipine
Angiotensin/converting enzyme inhibitor[2‡]	enalapril
Thiazides	trichlormethiazide, hydrochlorothiazide[3,5], benzylhydrochlorothiazide/reserpine/carbazochrome, mefruside, telmisartan/hydrochlorothiazide, valsartan/hydrochlorothiazide, candesartan/hydrochlorothiazide, candesartan/trichlormethiazide, losartan/hydrochlorothiazide
NSAIDs	diclofenac[2], celecoxib, loxoprofen, etodolac, nabumetone, pranoprofen
Anti-rheumatics	actarit, iguratimod, tofacitinib, penicillamine[2–5], leflunomide[1,3], sodium aurothiomalate[2–6#], bucillamine
Leukotriene receptor antagonist[2*]	pranlukast
5-ASA	mesalazine, salazosulfapyridine[5]
Tricyclic antidepressant	Imipramine[5], cromipramine, maprotiline
Antiepileptics	valproate, phenytoin[2,3,5], ethotoin, carbamazepine[2–5], zonisamide
Interferon[1,2,3]	interferon/alpha/2b, interferon/alpha, interferon/beta/1a, interferon/beta, interferon/gamma/1a, PEG/interferon/alpha/2a, PEG/interferon/alpha/2b
Immunogloblin[6]	thymoglobuline, zetbulin
Sulfamethoxazole/trimethoprim	sulfamethoxazole/trimethoprim[2]
Quinolones	levofloxacin, garenoxacin, moxifloxacin, pazufloxacin, tosufloxacin, sitafloxacin, ofloxacin, ciprofloxacin[2], norfloxacin, prulifloxacin, lomefloxacin
Tetracyclines	minocycline[2,3]
Beta-lactams	penicillin[2,5] (augmentin, amoxicillin, sultamicillin, piperacillin/tazobactam, piperacillin); cephalosporin[2] (cefoperazone/sulbactam, cefaclor, cefazolin, cefalexin, cefalotin, cefixime, cefepime, cefozopran, cefotaxime, cefotiam, cefoperazone, cefcapene, cefditoren, cefdinir, ceftazidime, ceftizoxime, ceftibuten, cefteram, ceftriaxone, cefpirome, cefpodoxime, cefminox, cefmetazole, cefmenoxime, cefroxadine, cefuroxime, flomoxef, latamoxef); penem (imipenem/cilastatin, tebipenem, doripenem, panipenem/betamipron, biapenem, faropenem, meropenem)
Anti-tuberculosis drugs	streptomycin, rifampicin[2], isonicotinyl hydrazide methanesulfonate, isoniazid[2,3,5], ethambutol
EGFR inhibitors	afatinib, erlotinib[1,3], gefitinib[1–3,6]
Molecular targeted drugs	imatinib[1,3], sunitinib[6], sorafenib, vandetanib, pazopanib, bortezomib, lapatinib
Anti PD-1 antibody	nivolumab[1]
Anti CTLA4 antibody	ipilimumab[1]
mTOR inhibitor[1]	everolimus

Platinum	oxaliplatin[6], carboplatin[6], cisplatin[6], nedaplatin, miliplatin
Topoisomerases	irinotecan[1,6], nogitecan, etoposide[3,6], sobuzoxane
Pyrimidine	capecitabine, gemcitabine[1–3,6], cytarabine ocfosfate, cytarabine[2,3,6], tegafur/gimeracil/oteracil, 5-fluorouracil[4,6], trifluridine, doxifluridine
Anthracyclines	amrubicin, epirubicin, adriamycin[4], doxorubicin[2,3,6], pirarubicin, mitoxantrone
Biological products	infliximab[2,3,6], adalimumab[2,3], abatacept, ustekinumab, etanercept, golimumab, certolizumab, ofatumumab, gemtuzumab, trastuzumab[3], trastuzumab emtansine, panitumumab[1], bevacizumab[3], mogamulizumab, rituximab[1,3,6], tocilizumab[1]
Microtubule polymerisation inhibitors	eribulin, vinblastine[2–4,6], docetaxel[1,3,6], nab-paclitaxel, paclitaxel[2,3,6], vinorelbine[6], vindesine[4,6]
Purine metabolism antagonists	azathioprine[3,4,6], mizoribine, cladribine, fludarabine[3,6]
Folic acid antagonists	methotrexate[1–6], pemetrexed[1]
DNA synthesis inhibitors	bleomycin[1–6], peplomycin, mitomycin[2–4,6]
Hormone therapy drugs	goserelin, degarelix, leuprorelin[6], danazol, bicalutamide, flutamide[3], anastrozole, tamoxifen
Alkylators	ifosfamide, cyclophosphamide[1–4,6], temozolomide, nimustine, busulfan[3,4,6], procarbazine[3,4,5], bendamustine, melphalan[3,4,6], ranimustine
Cytokine[6**]	celmoleukin
Thalidomide	thalidomide[3]
Retinoid	tretinoin[2,6]
BCG[3]	immucyst

NSAIDs: non-steroidal anti-inflammatory drugs; 5-ASA: 5-aminosalicylic acid; GCSF: granulocyte-colony stimulating factor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; PD-1: programmed cell death 1; CTLA4: cytotoxic T-lymphocyte-associated antigen 4; DNA: deoxyribonucleic acid; BCG: Bacille Calmette Guerin

†, referred to lidocaine; ‡, referred to captopril; #, referred to as gold or gold salts; *, referred to zafirleukast; **, referred to IL-2 and Tumor necrosis factor

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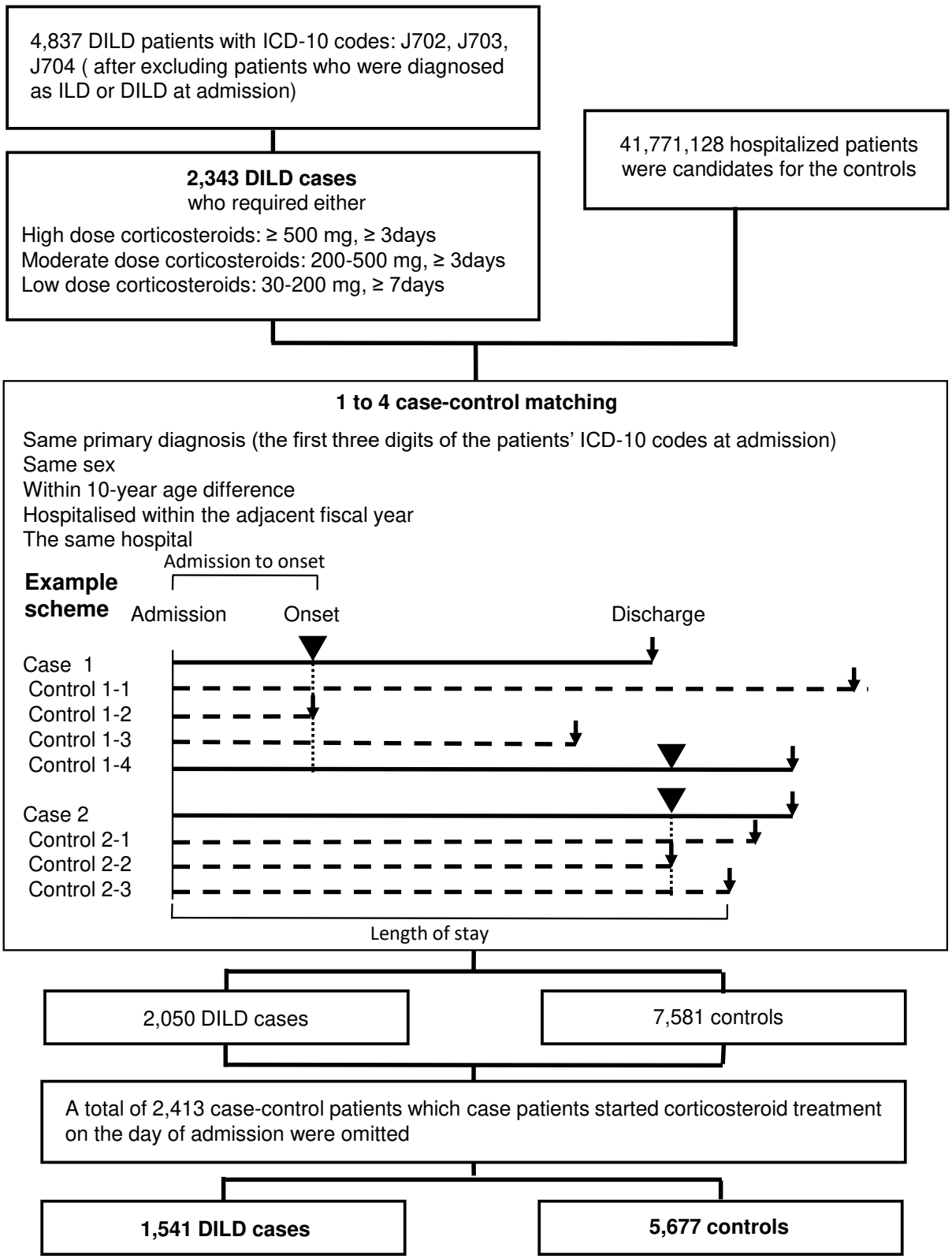
e-Tables 2. Population of patients prescribed drugs with potential risk during hospitalisation

Drug category with potential risk	Prescribed during hospitalisation				Prescribed before corticosteroids during hospitalisation			
	Cases (n = 1,541)		Controls (n = 5,677)		Cases (n = 1,541)		Controls (n = 5,677)	
	n	%	n	%	n	%	n	%
Antiplatelets	111	7.2	353	6,2	44	2.9	150	2.6
Anticoagulants	14	0.9	34	0.6	7	0.5	11	0.2
Statins	200	13	763	13	60	3.9	294	5.2
Sodium channel blockers	27	1.8	67	1.2	10	0.6	30	0.5
Beta blocker	0	0	1	0.01	0	0	1	0.02
Class III antiarrhythmic drugs	70	4.5	72	1.3	45	2.9	36	0.6
Calcium channel blockers	19	1.2	49	0.9	5	0.3	17	0.3
Angiotensin/converting enzyme inhibitor	46	3.0	173	3.0	16	1.0	73	1.3
Thiazides	43	2.8	159	2.8	11	0.7	67	1.2
NSAIDs	791	51	2159	38	360	23	952	17
Anti-rheumatics	5	0.3	27	0.5	1	0.06	6	0.1
Leukotriene receptor antagonist	5	0.3	33	0.6	0	0	6	0.1
5-ASA	20	1.2	47	0.8	3	0.2	10	0.2
Tricyclic antidepressant	5	0.3	16	0.3	1	0.06	8	0.1
Antiepileptics	42	2.7	170	3.0	16	1.0	53	0.9
Interferon	2	0.1	12	0.2	2	0.1	8	0.1
Immunogloblin	1	0.1	1	0.02	0	0	0	0
Sulfamethoxazole/trimethoprim	921	60	433	7.6	30	1.9	47	0.8
Quinolones	662	43	1106	19	175	11	246	4.3
Tetracyclines	117	7.6	167	2.9	41	2.7	71	1.3
Beta-lactams	1274	83	3460	61	639	41	1942	34
Anti-tuberculosis drugs	53	3.4	67	1.2	14	0.9	28	0.5
EGFR inhibitors	109	7.1	226	4.0	76	4.9	109	1.9
Molecular targeted drugs	23	1.5	55	1.0	3	0.2	7	0.1
Anti PD-1 antibody	1	0.06	2	0.03	1	0.06	1	0.02
Anti CTLA4 antibody	0	0	0	0	0	0	0	0
mTOR inhibitor	3	0.2	7	0.1	2	0.1	5	0.09
Platinum	114	7.4	663	12	4	0.3	11	0.2
Topoisomerases	51	3.3	221	3.9	3	0.2	5	0.09
Pyrimidine	121	7.9	338	6.0	16	1.0	54	1.0
Anthracyclines	51	3.3	132	2.3	9	0.6	12	0.2
Biological products	45	2.9	198	3.5	3	0.2	5	
Microtubule polymerisation inhibitors	147	9.5	378	6.7	4	0.3	11	0.09
Purine metabolism antagonists	6	0.4	21	0.4	0	0	2	0.04
Folic acid antagonists	59	3.8	249	4.4	3	0.2	4	0.07
DNA synthesis inhibitors	4	0.3	5	0.09	1	0.06	3	0.05
Hormone therapy drugs	18	1.2	34	0.6	8	0.5	10	0.17
Alkylators	69	4.5	118	2.1	0	0	4	0.07
Cytokine	0	0	0	0	0	0	0	0
Thalidomide	1	0.06	5	0.09	0	0	1	0.02
Retinoid	0	0	2	0.04	0	0	0	0

BCG	1	0.06	0	0	0	0	0	0

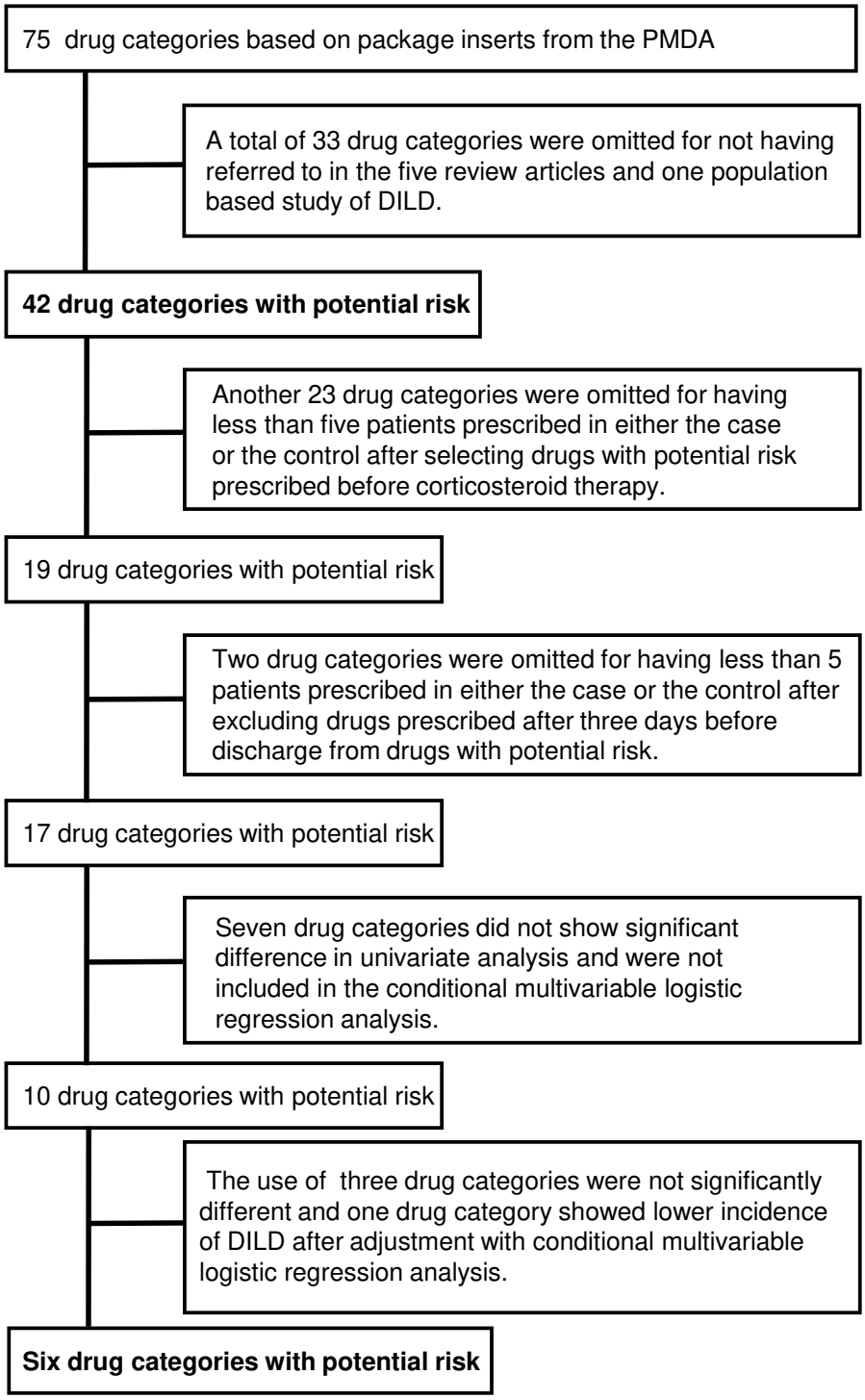
NSAIDs: non-steroidal anti-inflammatory drugs; 5-ASA: 5-aminosalicylic acid; EGFR: epidermal growth factor receptor; PD-1: programmed cell death 1; CTLA4: cytotoxic T-lymphocyte-associated antigen 4; DNA: deoxyribonucleic acid; BCG: Bacille Calmette Guerin

e-Figure 1



A flow diagram of DILD case and controls. Case patients were 1 to 4 matched to control patients.
As shown in the example scheme, case patients were matched to control patients with length of stay longer than admission to onset in case patients. Case patients can be chosen as control. Case 2 is chosen as Control (Control 1-4) for Case 1 in the example scheme. Case patient were not necessarily matched to four patients if not possible as shown in Case 2.
DILD: drug-induced interstitial lung disease

e-Figure 2



A flow diagram of causative drugs for drug-induced interstitial lung disease.
PMDA: the Pharmaceuticals and Medical Devices Agency

e-Table 1. Drug classification

Category Name	Generic Name
Antiplatelets	clopidogrel, cilostazol, ticlopidine[2], beraprost, beraprost–long acting, complavin
Anticoagulants [2,3]	dabigatran
Statins[1,2,3]	atorvastatin[2], simvastatin, pitavastatin, fluvastatin, pravastatin, rosuvastatin, amlodipine/atorvastatin
Sodium channel blockers[4,5†]	mexiletine, aprindine, cibenzoline
Beta blocker	acebutolol[2]
Class III antiarrhythmic drugs	amiodarone[1–6]
Calcium channel blockers	bepridil[1], amlodipine/atorvastatin, telmisartan/amlodipine, valsartan/amlodipine, valsartan/cilnidipine, candesartan/amlodipine
Angiotensin/converting enzyme inhibitor[2‡]	enalapril
Thiazides	trichlormethiazide, hydrochlorothiazide[3,5], benzylhydrochlorothiazide/reserpine/carbazochrome, mefruside, telmisartan/hydrochlorothiazide, valsartan/hydrochlorothiazide, candesartan/hydrochlorothiazide, candesartan/trichlormethiazide, losartan/hydrochlorothiazide
NSAIDs	diclofenac[2], celecoxib, loxoprofen, etodolac, nabumetone, pranoprofen
Anti-rheumatics	actarit, iguratimod, tofacitinib, penicillamine[2–5], leflunomide[1,3], sodium aurothiomalate[2–6#], bucillamine
Leukotriene receptor antagonist[2*]	pranlukast
5-ASA	mesalazine, salazosulfapyridine[5]
Tricyclic antidepressant	Imipramine[5], cromipramine, maprotiline
Antiepileptics	valproate, phenytoin[2,3,5], ethotoin, carbamazepine[2–5], zonisamide
Interferon[1,2,3]	interferon/alpha/2b, interferon/alpha, interferon/beta/1a, interferon/beta, interferon/gamma/1a, PEG/interferon/alpha/2a, PEG/interferon/alpha/2b
Immunogloblin[6]	thymoglobuline, zetbulin
Sulfamethoxazole/trimethoprim	sulfamethoxazole/trimethoprim[2]
Quinolones	levofloxacin, garenoxacin, moxifloxacin, pazufloxacin, tosufloxacin, sitafloxacin, ofloxacin, ciprofloxacin[2], norfloxacin, prulifloxacin, lomefloxacin
Tetracyclines	minocycline[2,3]
Beta-lactams	penicillin[2,5] (augmentin, amoxicillin, sultamicillin, piperacillin/tazobactam, piperacillin); cephalosporin[2] (cefoperazone/sulbactam, cefaclor, cefazolin, cefalexin, cefalotin, cefixime, cefepime, cefozopran, cefotaxime, cefotiam, cefoperazone, cefcapene, cefditoren, cefdinir, ceftazidime, ceftizoxime, ceftibuten, cefteram, ceftriaxone, cefpirome, cefpodoxime, cefminox, cefmetazole, cefmenoxime, cefroxadine, cefuroxime, flomoxef, latamoxef); penem (imipenem/cilastatin, tebipenem, doripenem, panipenem/betamipron, biapenem, faropenem, meropenem)
Anti-tuberculosis drugs	streptomycin, rifampicin[2], isonicotinyl hydrazide methanesulfonate, isoniazid[2,3,5], ethambutol
EGFR inhibitors	afatinib, erlotinib[1,3], gefitinib[1–3,6]
Molecular targeted drugs	imatinib[1,3], sunitinib[6], sorafenib, vandetanib, pazopanib, bortezomib, lapatinib
Anti PD-1 antibody	nivolumab[1]
Anti CTLA4 antibody	ipilimumab[1]
mTOR inhibitor[1]	everolimus

Platinum	oxaliplatin[6], carboplatin[6], cisplatin[6], nedaplatin, miliplatin
Topoisomerases	irinotecan[1,6], nogitecan, etoposide[3,6], sobuzoxane
Pyrimidine	capecitabine, gemcitabine[1–3,6], cytarabine ocfosfate, cytarabine[2,3,6], tegafur/gimeracil/oteracil, 5-fluorouracil[4,6], trifluridine, doxifluridine
Anthracyclines	amrubicin, epirubicin, adriamycin[4], doxorubicin[2,3,6], pirarubicin, mitoxantrone
Biological products	infliximab[2,3,6], adalimumab[2,3], abatacept, ustekinumab, etanercept, golimumab, certolizumab, ofatumumab, gemtuzumab, trastuzumab[3], trastuzumab emtansine, panitumumab[1], bevacizumab[3], mogamulizumab, rituximab[1,3,6], tocilizumab[1]
Microtubule polymerisation inhibitors	eribulin, vinblastine[2–4,6], docetaxel[1,3,6], nab-paclitaxel, paclitaxel[2,3,6], vinorelbine[6], vindesine[4,6]
Purine metabolism antagonists	azathioprine[3,4,6], mizoribine, cladribine, fludarabine[3,6]
Folic acid antagonists	methotrexate[1–6], pemetrexed[1]
DNA synthesis inhibitors	bleomycin[1–6], peplomycin, mitomycin[2–4,6]
Hormone therapy drugs	goserelin, degarelix, leuprorelin[6], danazol, bicalutamide, flutamide[3], anastrozole, tamoxifen
Alkylators	ifosfamide, cyclophosphamide[1–4,6], temozolomide, nimustine, busulfan[3,4,6], procarbazine[3,4,5], bendamustine, melphalan[3,4,6], ranimustine
Cytokine[6**]	celmoleukin
Thalidomide	thalidomide[3]
Retinoid	tretinoin[2,6]
BCG[3]	immucyst

NSAIDs: non-steroidal anti-inflammatory drugs; 5-ASA: 5-aminosalicylic acid; GCSF: granulocyte-colony stimulating factor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; PD-1: programmed cell death 1; CTLA4: cytotoxic T-lymphocyte-associated antigen 4; DNA: deoxyribonucleic acid; BCG: Bacille Calmette Guerin

†, referred to lidocaine; ‡, referred to captopril; #, referred to as gold or gold salts; *, referred to zafirleukast; **, referred to IL-2 and Tumor necrosis factor

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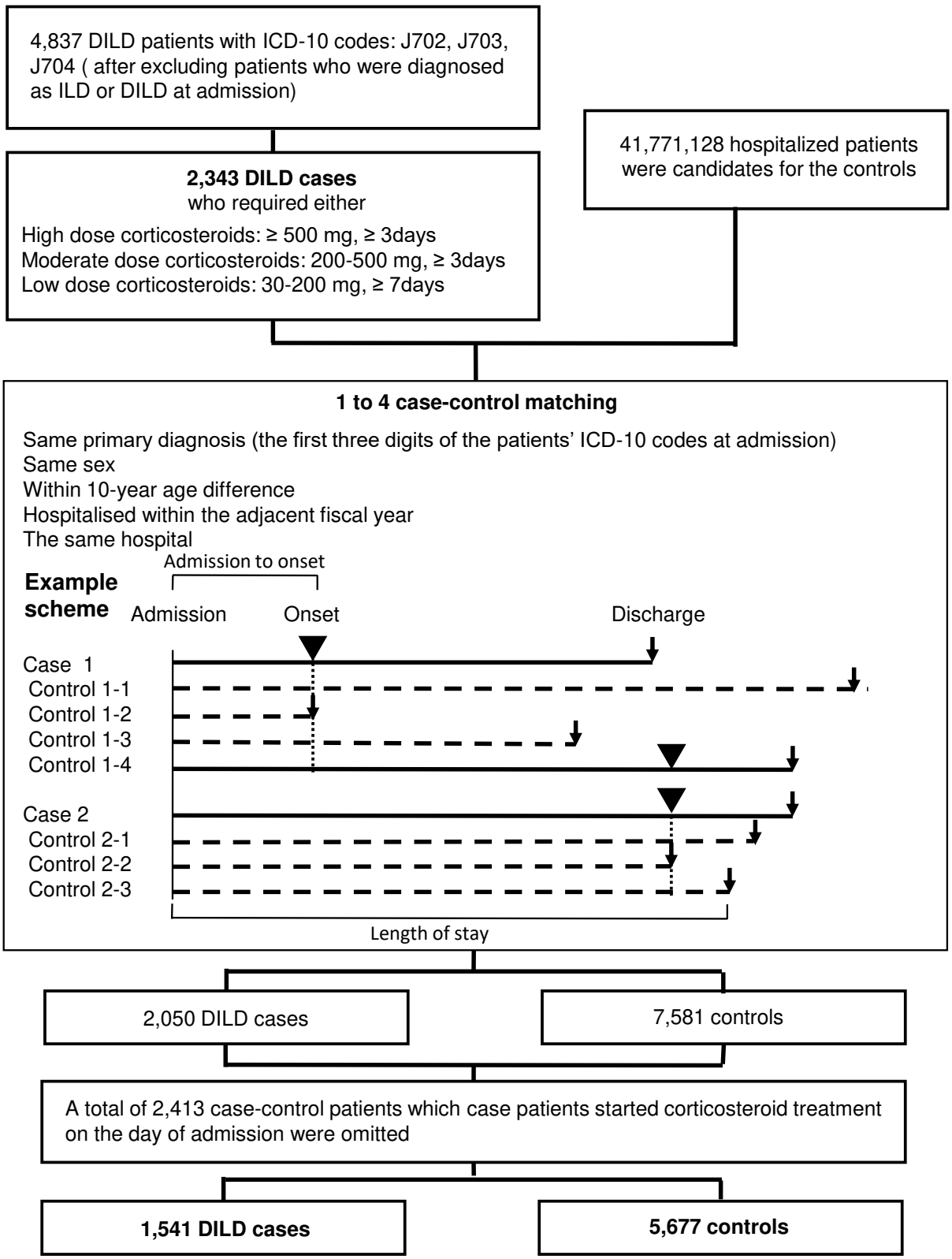
e-Tables 2. Population of patients prescribed drugs with potential risk during hospitalisation

Drug category with potential risk	Prescribed during hospitalisation				Prescribed before corticosteroids during hospitalisation			
	Cases (n = 1,541)		Controls (n = 5,677)		Cases (n = 1,541)		Controls (n = 5,677)	
	n	%	n	%	n	%	n	%
Antiplatelets	111	7.2	353	6,2	44	2.9	150	2.6
Anticoagulants	14	0.9	34	0.6	7	0.5	11	0.2
Statins	200	13	763	13	60	3.9	294	5.2
Sodium channel blockers	27	1.8	67	1.2	10	0.6	30	0.5
Beta blocker	0	0	1	0.01	0	0	1	0.02
Class III antiarrhythmic drugs	70	4.5	72	1.3	45	2.9	36	0.6
Calcium channel blockers	19	1.2	49	0.9	5	0.3	17	0.3
Angiotensin/converting enzyme inhibitor	46	3.0	173	3.0	16	1.0	73	1.3
Thiazides	43	2.8	159	2.8	11	0.7	67	1.2
NSAIDs	791	51	2159	38	360	23	952	17
Anti-rheumatics	5	0.3	27	0.5	1	0.06	6	0.1
Leukotriene receptor antagonist	5	0.3	33	0.6	0	0	6	0.1
5-ASA	20	1.2	47	0.8	3	0.2	10	0.2
Tricyclic antidepressant	5	0.3	16	0.3	1	0.06	8	0.1
Antiepileptics	42	2.7	170	3.0	16	1.0	53	0.9
Interferon	2	0.1	12	0.2	2	0.1	8	0.1
Immunogloblin	1	0.1	1	0.02	0	0	0	0
Sulfamethoxazole/trimethoprim	921	60	433	7.6	30	1.9	47	0.8
Quinolones	662	43	1106	19	175	11	246	4.3
Tetracyclines	117	7.6	167	2.9	41	2.7	71	1.3
Beta-lactams	1274	83	3460	61	639	41	1942	34
Anti-tuberculosis drugs	53	3.4	67	1.2	14	0.9	28	0.5
EGFR inhibitors	109	7.1	226	4.0	76	4.9	109	1.9
Molecular targeted drugs	23	1.5	55	1.0	3	0.2	7	0.1
Anti PD-1 antibody	1	0.06	2	0.03	1	0.06	1	0.02
Anti CTLA4 antibody	0	0	0	0	0	0	0	0
mTOR inhibitor	3	0.2	7	0.1	2	0.1	5	0.09
Platinum	114	7.4	663	12	4	0.3	11	0.2
Topoisomerases	51	3.3	221	3.9	3	0.2	5	0.09
Pyrimidine	121	7.9	338	6.0	16	1.0	54	1.0
Anthracyclines	51	3.3	132	2.3	9	0.6	12	0.2
Biological products	45	2.9	198	3.5	3	0.2	5	
Microtubule polymerisation inhibitors	147	9.5	378	6.7	4	0.3	11	0.09
Purine metabolism antagonists	6	0.4	21	0.4	0	0	2	0.04
Folic acid antagonists	59	3.8	249	4.4	3	0.2	4	0.07
DNA synthesis inhibitors	4	0.3	5	0.09	1	0.06	3	0.05
Hormone therapy drugs	18	1.2	34	0.6	8	0.5	10	0.17
Alkylators	69	4.5	118	2.1	0	0	4	0.07
Cytokine	0	0	0	0	0	0	0	0
Thalidomide	1	0.06	5	0.09	0	0	1	0.02
Retinoid	0	0	2	0.04	0	0	0	0

BCG	1	0.06	0	0	0	0	0	0

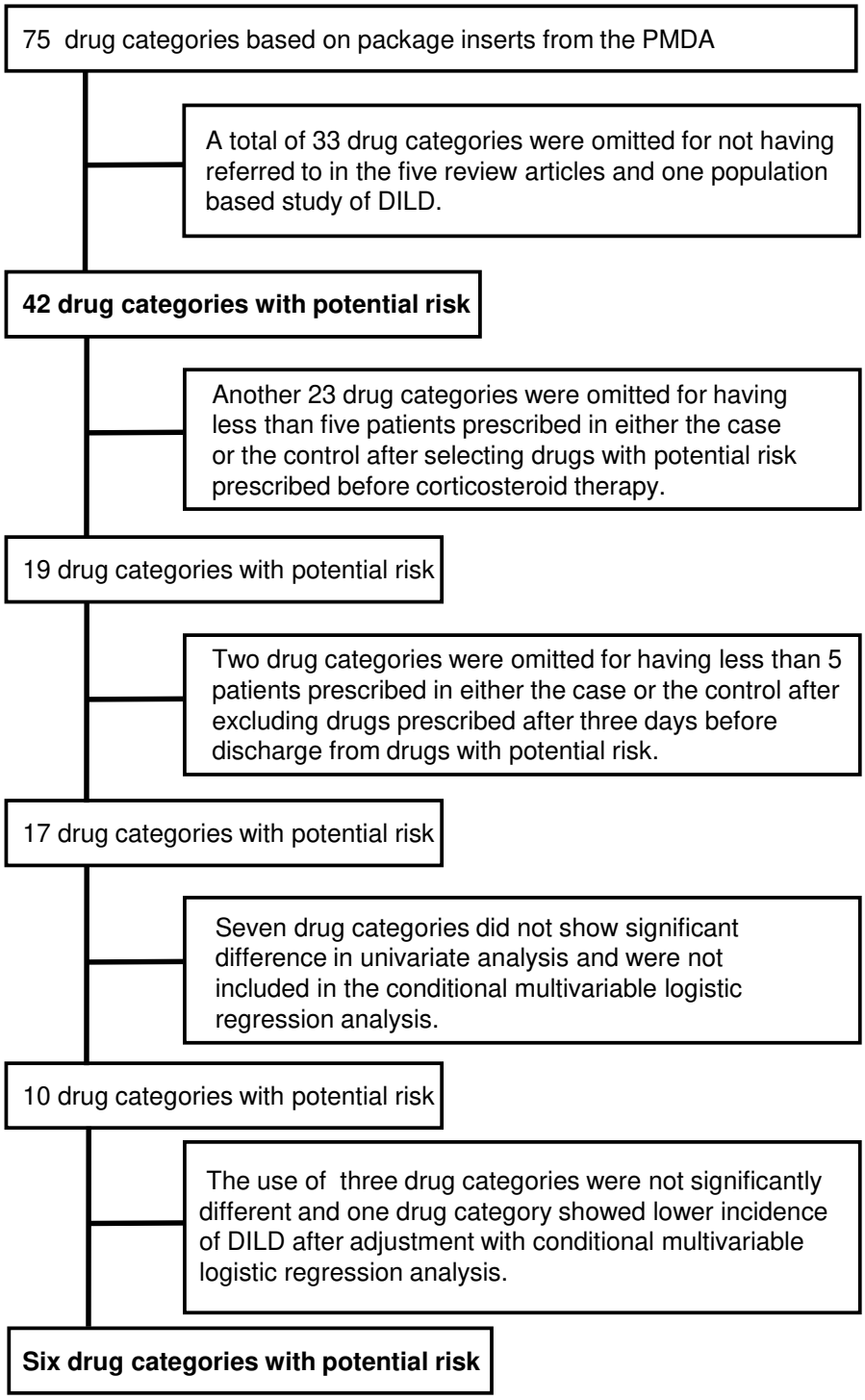
NSAIDs: non-steroidal anti-inflammatory drugs; 5-ASA: 5-aminosalicylic acid; EGFR: epidermal growth factor receptor; PD-1: programmed cell death 1; CTLA4: cytotoxic T-lymphocyte-associated antigen 4; DNA: deoxyribonucleic acid; BCG: Bacille Calmette Guerin

e-Figure 1



A flow diagram of DILD case and controls. Case patients were 1 to 4 matched to control patients.
As shown in the example scheme, case patients were matched to control patients with length of stay longer than admission to onset in case patients. Case patients can be chosen as control. Case 2 is chosen as Control (Control 1-4) for Case 1 in the example scheme. Case patient were not necessarily matched to four patients if not possible as shown in Case 2.
DILD: drug-induced interstitial lung disease

e-Figure 2



A flow diagram of causative drugs for drug-induced interstitial lung disease.
PMDA: the Pharmaceuticals and Medical Devices Agency