Risk factors and drugs that trigger the onset of Stevens–Johnson syndrome and toxic epidermal necrolysis: A population-based cohort study using the Shizuoka Kokuho database

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Background: Evidence of factors associated with Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) from population-based studies is scarce.

Objective: We aimed to identify the incidence, risk factors, and drugs that trigger the development of SJS/TEN in the general population.

Methods: A regional, population-based, longitudinal cohort with 2,398,393 Japanese individuals was analyzed using the Shizuoka Kokuho Database from 2012 to 2020.

Results: Among 1,909,570 individuals, 223 (0.01%, 2.3 cases/100,000 person-years) patients were diagnosed with SJS/TEN during the observational period of a maximum of 7.5 years. In a multivariable analysis, the risks of SJS/TEN were an older age, and the presence of type 2 diabetes, peripheral vascular disease, and systemic autoimmune diseases. The administration of drugs, such as immune checkpoint inhibitors, insulin, and type 2 diabetes agents, triggered the onset of SJS/TEN.

Limitations: The results may apply only to the Japanese population.

Conclusion: In this cohort population from a database representing the general population, the risks of developing SJS/TEN were old age and a history of type 2 diabetes, peripheral vascular disease, and systemic autoimmune disease. Furthermore, in addition to previously reported drugs, the administration of immune checkpoint inhibitors, insulin, and type 2 diabetes agents, may trigger the development of SJS/TEN. (JAAD Int 2023;11:24-32.)

Key words: claims database; drug eruption; population-based cohort study; pharmacoepidemiology; risk factor; safety; Stevens–Johnson syndrome; toxic epidermal necrolysis.

INTRODUCTION

Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) represent a spectrum of severe cutaneous adverse reactions,[1,2] and are clinically characterized by erythema, blistering, and erosions. SJS/TEN may also induce lung and liver damage,[3-5] causing life-threatening events and death in the worst-case scenario. Nevertheless, there are only

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limited data related to the incidence of SJS/TEN because of few longitudinal cohort studies. These studies have shown an incidence of 1 to 7 cases/million/year for SJS and 0.4 to 1.5 for TEN.[6,7] Previous studies have reported risk factors associated with SJS/TEN, such as skin disease, liver disease,[8] diabetes, psoriasis, systemic lupus erythematosus, and previous drug allergies.[9] However, these previous studies did not examine the risk factors using a cohort in the general population as a riskset.

Previous case series studies showed potential agents that cause the onset of SJS/TEN, such as anti-inflammatory analgesics, antibacterial agents, anticonvulsants, antigout agents, and anticancer agents (eg, immune checkpoint inhibitors).[10-15] However, the risk of drug administration for the onset of SJS/TEN has not been investigated using causal inference in cohort studies.

Therefore, we investigated the risk factors and drugs that trigger the onset of SJS/TEN using a large, population-based, longitudinal cohort from an insurance claims database (Shizuoka Kokuho Database [SKDB]).

CAPSULE SUMMARY

- Limited information regarding Stevens—Johnson syndrome or toxic epidermal necrolysis is available.
- Physicians may wish to consider risk factors, such as older age and diabetes, that may be associated with the development of Stevens—Johnson syndrome or toxic epidermal necrolysis, and drugs that trigger this disease such as immune-checkpoint inhibitors.

METHODS

Data resource

In this study, we used the SKDB with already cleaned data.[16] The data of all enrollees were anonymized.[16] The SKDB can be considered a regional, population-based, longitudinal cohort of 2,398,393 Japanese people (women, n = 1,303,667, 54.4%) living in Shizuoka Prefecture, near the center of Japan (population of approximately 3.6 million).[16] The SKDB has been used as a data source in several studies.[17-19] Comprehensive, personally linked data were collected, and everyone was assigned a unique identifier. This dataset includes basic information from the subscriber list (eg, sex, age, zip code, observation period, and reason for disenrollment including death) and claims from public health insurance organizations (<75 years old for the National Health Insurance system and >75 years old for the Latter-stage Elderly Medical Care System).

The SKDB is a suitable database for real-world studies because it contains accurate information on deaths and loss to follow-up from the Basic Resident Registration System. In addition, in this database, Anatomical Therapeutic Chemical classification codes and International Classification of Diseases, 10th Revision (ICD-10) codes are included for searching for drugs and diagnoses.

Population and observational period

We used a dataset of the SKDB that comprised 8.5 years of longitudinal data from April 2012 to September 2020. All enrollees were investigated using individually linked databases between their annual health checkups and medical claims. To clarify the risk factors for new-onset SJS/TEN, we excluded patients who had already been diagnosed with drug eruption, such as SJS/TEN and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, before the index date. The study schema is shown in Fig 1. Each enrollee's observation period was defined as the time from the date of insurance registration or 1 April 2012, whichever came earlier, to the date of insurance withdrawal or 30 September 2020, whichever came later.

Comorbidities as candidate risk factors associated with onset of SJS/TEN

Patients with SJS/TEN were defined as those with a medical claim with the disease code, which is the code used for billing medical fees for SJS/TEN (SJS: 6951003, TEN: 8845586). In this study, the candidate risk factors were age, sex, and the presence of comorbidities using the Elixhauser comorbidity index[20] and previously reported risk factors and candidate risk factors[8,9,21,22] (as defined using the ICD-10, Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/yd63zxsgxy/1).

Drugs as candidate risk factors associated with onset of SJS/TEN

To identify drugs that trigger the onset of SJS/TEN, we created a list of causative drugs for SJS/TEN and drug reaction with eosinophilia and systemic symptoms, analogous drugs with caution for drug eruptions in medication package inserts, and potential causative drugs, such as immune checkpoint inhibitors, insulin, and type 2 diabetes agents (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/yd63zxsgxy/1).

Abbreviations used:

CI:	confidential interval
HR:	hazard ratio
ICD-10:	International Classification of Disease, 10th revision
SJS:	Stevens–Johnson syndrome
SKDB:	Shizuoka Kokuho Database
TEN:	toxic epidermal necrolysis

Statistical analysis

The data are shown as the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. The Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables were performed for comparison between 2 groups.

Univariate and multivariable Cox regression analyses were performed to examine the factors associated with the onset of SJS/TEN. We calculated hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values in the Wald test. The reported risk factors (eg, age) and potential risk factors (eg, critical etiological and epidemiological factors) were used in the regression analysis. One (hypertension) of 2 variables with a high correlation was not used in the multivariable model owing to multicollinearity, based on the criterion of an absolute Spearman correlation coefficient >0.4. Because missing covariates did not occur completely at random among all patients, simple missing data imputation was not carried out. The variables with ≥10 cases of onset of SJS/TEN shown in Table I and a *P* value < .05 were selected as factors to be included in the multivariable regression model.

A risk classification (low, middle, and high) was constructed using the individual predictive value estimated from the multivariable Cox model. To examine the causal relationship between the administration of drugs and the subsequent onset of SJS/TEN, a Cox regression analysis was performed with the time to onset of SJS/TEN within 4 months[8,23] from the date of the first administration of each drug (or the index date if not administered). The onset of SJS/TEN can occur within 1 month after taking the triggered drugs, but to identify the triggered drugs based on causal inference, the maximum possible period until the onset was set at 4 months.

A *P*-value of < .05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute) and EZR version 1.55 (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html).[24]

RESULTS

Characteristics of patients with SJS/TEN

The procedure for extracting the first diagnosed SJS/TEN among all cases in the SKDB is shown in Fig 2. Among 1,909,570 individuals, the number of SJS/TEN cases that developed during the observation period was 223. The median (minimum-maximum) observation period was 6.0 (0-7.5) years, and the incidence of SJS/TEN onset was 2.3 cases/100,000 person-years.

The characteristics of patients with SJS/TEN at the time of diagnosis and other participants without SJS/TEN are shown in Table I. The patients who developed SJS/TEN were more likely to have an older age (>60 years) and a history of kidney disease, liver disease, gout, type 2 diabetes, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, deficiency anemia, depression, cardiac arrythmias, valvular disease, hypertension (uncomplicated), diabetes (complications), renal failure, peptic ulcer disease, solid tumor without metastasis, or systemic autoimmune disease than other individuals.

Identification of risk factors for the development of SJS/TEN

The results of univariable and multivariable regression analyses in the analysis set are shown in Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/yd63zxsgxy/1 and Table II. Hypertension was excluded because of its high correlation with age. Other variables with $P \leq .05$ were entered into the multivariable model. The multivariable analysis showed that age (60-<70 vs 0-40 years as a reference: HR: 1.94 [95% CI: 1.04-3.51], 70-80: 2.91 [1.57-5.23], >80: 1.91 [1.01-3.62]), the presence of type 2 diabetes (1.53 [1.01-2.32]), peripheral vascular disease (1.76 [1.24-2.51]), and systemic autoimmune disease (1.80 [1.07-3.03]) increased the risk of developing SJS/TEN.

Identification of drugs that trigger the development of SJS/TEN

The frequency of potential drug use during the 4 months before SJS/TEN was determined by classifying them into risk categories (low, middle, and high, Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/yd63zxsgxy/1). We found that patients at a high risk of developing SJS/TEN had a higher rate of using anticonvulsants, antiarrhythmics drugs, sulfa drugs, antigout agents, immune checkpoint inhibitors, antifungals, mucolytic agents, anti-cancer drugs, antipsychotics, insulin, and type-2 diabetes agents than

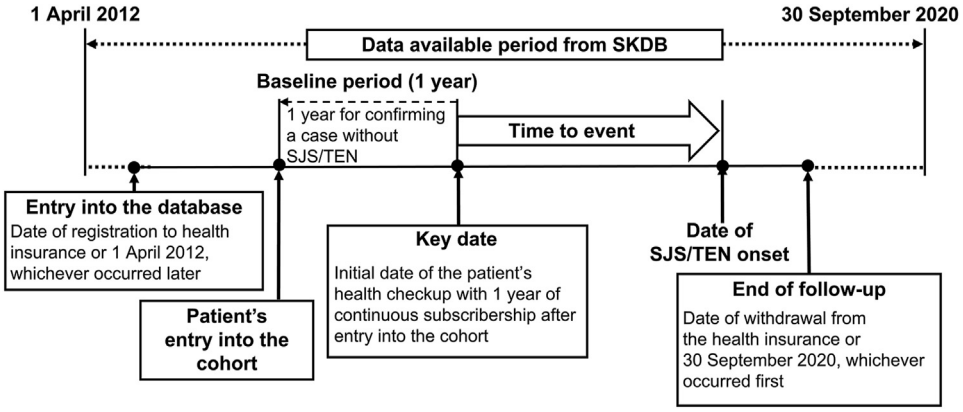

Fig 1. Study schema. Cohort entry is the date of registration with the health insurance provider or April 1, 2012, whichever occurred later. The index date is the initial date with ≥1-year continuous subscribership to the health insurance system. The follow-up period is the interval between the index date and (1) the end of the study (September 30, 2020), or (2) the withdrawal date from the health insurance system, whichever occurred first. *SJS/TEN*, Stevens–Johnson syndrome and toxic epidermal necrolysis; *SKDB*, Shizuoka Kokuho Database.

those at a low risk, but not antibacterials and nonsteroidal anti-inflammatory drugs.

The results of univariable and multivariable regression analyses on the causal relationship between drugs and the onset of SJS/TEN are shown in Table III. In the multivariable analysis, the administration of drugs other than antiarrhythmics increased the risk of SJS/TEN onset. In particular, the drugs with an HR of >50 were anticonvulsants (HR: 66.97 [95% CI: 29.99-149.50]), immune checkpoint inhibitors (486.70 [175.70-1348.00]), anticancer drugs (50.02 [21.77-115.00]), and insulin (73.36 [33.80-159.20]).

DISCUSSION

This large-scale cohort study clarified the risk factors for SJS/TEN. We found that the incidence of SJS/TEN was 2.3 cases/100,000 person-years. The risk factors for the onset of SJS/TEN were an old age (>60 years) and a history of type 2 diabetes, peripheral vascular disease, and systemic autoimmune disease. Additionally, the drugs that triggered the development of SJS/TEN were anticonvulsants, sulfa drugs, antigout agents, antibacterial agents, nonsteroidal anti-inflammatory drugs, antifungals, mucolytic agents, anticancer drugs, antipsychotics, immune checkpoint inhibitors, insulin, and type 2 diabetes agents. These results could contribute to the early diagnosis and prevention of the onset of SJS/TEN in the future, and such information was not available from previous reports.

SJS and TEN, which are differently defined on the basis of affected skin areas, represent a spectrum of severe cutaneous adverse reactions characterized by extended epidermal necrosis. There are several key factors involved in the pathogenesis of SJS/TEN, such as drug-reactive cytotoxic CD8+ T-lymphocytes[25] and soluble biomolecules, including Fas-ligand,[26] granulysin,[26] and annexin-A1,[27] and neutrophil extracellular traps.[28] Although the mechanism of SJS/TEN has been recently determined,[25-28] the appropriate early therapeutic intervention is unknown. Furthermore, the mortality of SJS/TEN has worsened in the last decade.[6] Therefore, identifying risk factors for developing SJS/TEN is important or early therapeutic intervention.

Older people tend to use various medicines for a number of diseases that they suffer from. Additionally, such a situation for older people may promote desynchronized T-cell activation under a microenvironment with development of cytotoxicity by senescence,[29,30] which could be associated with a high incidence of SJS/TEN.

In this study, we showed that 3 underlying diseases were associated with the development of SJS/TEN, namely systemic autoimmune disease and type 2 diabetes, as previously shown,[9] and peripheral vascular disease. In autoimmune disease, disturbed regulatory immunity augments cytotoxic reactions, which are associated with the induction of SJS/TEN.[31,32] Diabetes often causes internal organ damage, such as that to the kidney and liver, leading to increased drug concentrations by impaired metabolizing activity, and this might be associated with the augmentation of hypersensitivity reactions. Peripheral vascular disease (eg, ICD-10 codes I70, I71, I731, I738,

Table I. Characteristics of patients with onset of SJS/TEN

Variable	Category or unit	SJS/TEN (n = 223)	Others (n = 1,909,347)	P value
Age (y)	1	69.46 ± 14.78	57.46 ± 23.42	<.001
Age (y)	0 to <40	14 (6.3)	450,724 (23.6)	<.001
	40 to <50	7 (3.1)	142,411 (7.5)	
	50 to <60	8 (3.6)	155,583 (8.1)	
	60 to <70	56 (25.1)	456,473 (23.9)	
	70 to <80	98 (43.9)	429,628 (22.5)	
	≥80	40 (17.9)	274,528 (14.4)	
Sex	Women	116 (52.0)	1,031,695 (54.0)	.546
Allergy disease	Presence	69 (30.9)	502,906 (26.3)	.128
Dermatological disease	Presence	79 (35.4)	487,342 (25.5)	.001
Kidney disease	Presence	38 (17.0)	138,766 (7.3)	<.001
Liver disease	Presence	40 (17.9)	184,542 (9.7)	<.001
Gout	Presence	32 (14.3)	140,851 (7.4)	<.001
Mycoplasma infection	Presence	0 (0.0)	4019 (0.2)	>.999
HHV infection	Presence	6 (2.7)	25,811 (1.4)	.132
Psoriasis	Presence	2 (0.9)	10,903 (0.6)	.364
Drug allergy	Presence	0 (0.0)	0 (0.0)	NA
Type-1 diabetes	Presence	0 (0.0)	2544 (0.1)	>.999
Type-2 diabetes	Presence	28 (12.6)	99,036 (5.2)	<.001
AIDS/HIV	Presence	1 (0.4)	332 (0.0)	.038
Congestive heart failure	Presence	40 (17.9)	160,246 (8.4)	<.001
Peripheral vascular disease	Presence	44 (19.7)	128,233 (6.7)	<.001
Chronic pulmonary disease	Presence	51 (22.9)	335,373 (17.6)	.043
Hemiplegia or paraplegia	Presence	2 (0.9)	15,950 (0.8)	.771
Metastatic solid tumor	Presence	5 (2.2)	16,594 (0.9)	.046
Weight loss	Presence	0 (0.0)	5944 (0.3)	>.999
Fluid and electrolyte disorders	Presence	23 (10.3)	141,972 (7.4)	.123
Deficiency anemia	Presence	24 (10.8)	110,284 (5.8)	.004
Alcohol abuse	Presence	0 (0.0)	8614 (0.5)	.631
Drug abuse	Presence	0 (0.0)	632 (0.0)	>.999
Depression	Presence	18 (8.1)	92,603 (4.8)	.040
Psychoses	Presence	7 (3.1)	46,934 (2.5)	.510
Cardiac arrythmia	Presence	36 (16.1)	165,450 (8.7)	<.001
Valvular disease	Presence	12 (5.4)	56,709 (3.0)	.045
Pulmonary circulation disorders	Presence	1 (0.4)	3915 (0.2)	.367
Hypertension, uncomplicated	Presence	124 (55.6)	659,825 (34.6)	<.001
Hypertension, complicated	Presence	2 (0.9)	12,204 (0.6)	.657
Other neurological disorders	Presence	13 (5.8)	72,441 (3.8)	.113
Diabetes, no complications	Presence	9 (4.0)	24,726 (1.3)	.003
Diabetes, complications	Presence	20 (9.0)	75,544 (4.0)	.001
Hypothyroidism	Presence	6 (2.7)	29,320 (1.5)	.163
Renal failure	Presence	11 (4.9)	45,353 (2.4)	.023
Liver disease	Presence	44 (19.7)	195,870 (10.3)	<.001
Peptic ulcer disease	Presence	56 (25.1)	237,060 (12.4)	<.001
Lymphoma	Presence	2 (0.9)	5906 (0.3)	.152
Solid tumor without metastasis	Presence	28 (12.6)	116,459 (6.1)	<.001
Systemic autoimmune diseases	Presence	16 (7.2)	49,041 (2.6)	<.001
Coagulopathy	Presence	6 (2.7)	13,908 (0.7)	.006
Obesity	Presence	2 (0.9)	5804 (0.3)	.148
Blood loss anemia	Presence	2 (0.9)	2876 (0.2)	.045

Data are shown as the mean ± standard deviation or *n* (%).

AIDS, Acquired immunodeficiency syndrome; *HHV*, human herpesvirus; *HIV*, human immunodeficiency virus; *SJS/TEN*, Stevens–Johnson syndrome and toxic epidermal necrolysis.

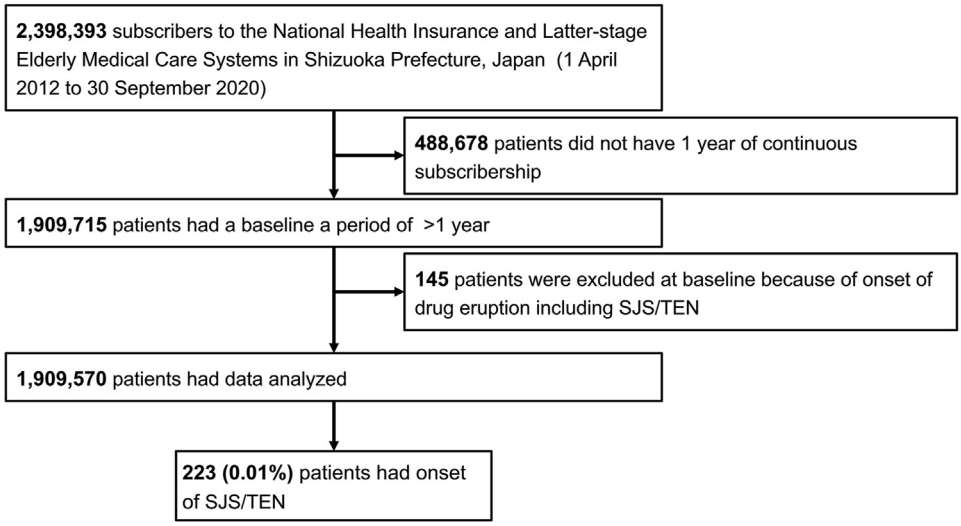

Fig 2. Flow chart of the patients. The population as an analysis set of this study excluded patients with a baseline period of <1 year and patients diagnosed with drug eruption, such as SJS/TEN and DIHS/DRESS, before the start date of the health examination from all registrants from April 2012 to September 2020. *DIHS*, Drug-induced hypersensitivity syndrome; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *SJS/TEN*, Stevens–Johnson syndrome and toxic epidermal necrolysis.

Table II. Multivariable Cox regression analysis of the onset of SJS/TEN

		Multivariable model		
Variable (reference)	**Category**	**HR**	**95% CI**	***P* value**
Age (0 to <40 y)	40 to <50 y	1.16	0.47-2.88	.749
	50 to <60 y	1.00	0.41-2.38	.999
	60 to <70 y	**1.94**	**1.04-3.51**	**.030**
	70 to <80 y	**2.91**	**1.57-5.23**	**<.001**
	≥80 y	**1.91**	**1.01-3.62**	**.046**
Sex (women)	Men	0.87	0.66-1.15	.319
Dermatological disease (absence)	Presence	1.22	0.92-1.62	.173
Kidney disease (absence)	Presence	1.41	0.96-2.07	.077
Liver disease (absence)	Presence	1.17	0.82-1.67	.376
Gout (absence)	Presence	1.15	0.77-1.73	.498
Type-2 diabetes (absence)	Presence	**1.53**	**1.01-2.32**	**.043**
Congestive heart failure (absence)	Presence	1.29	0.88-1.92	.192
Peripheral vascular disease (absence)	Presence	**1.76**	**1.24-2.51**	**.002**
Deficiency anemia (absence)	Presence	1.15	0.73-1.80	.551
Depression (absence)	Presence	1.35	0.83-2.20	.231
Cardiac arrythmia (absence)	Presence	1.04	0.71-1.54	.827
Peptic ulcer disease (absence)	Presence	1.27	0.91-1.75	.156
Solid tumor without metastasis (absence)	Presence	1.39	0.92-2.09	.122
Systemic autoimmune disease (absence)	Presence	**1.80**	**1.07-3.03**	**.027**

Bold type indicates statistical significance.
CI, Confidence interval; *HR*, hazard ratio.

I739, I771, I790, I792, K551, K558, K559, Z958, and Z959) is an ambiguous category including intermittent claudication, peripheral angiopathy (not otherwise specified), and spasm of an artery. Therefore, the reason for this association remains unclear and it requires further investigation.

Surprisingly, we found that the use of immune checkpoint inhibitors had an extremely high HR (>400) in the incidence of SJS/TEN compared with nonusers. This HR was the highest among the investigated drugs, and the presence of malignancy was not associated with the incidence of SJS/TEN

Table III. Cox regression analysis of the incidence of SJS/TEN by a drug taken within 4 months

Drug taken within 4 mo	Incidence of SJS/TEN within 4 mo of taking the drug (%)	Incidence of SJS/TEN within 4 mo of not taking the drug (%)	Univariable model			Multivariable model		
			HR	95% CI	*P* value	HR	95% CI	*P* value
Anticonvulsant	0.036	<0.001	**76.95**	**35.03-169.00**	**<.001**	**66.97**	**29.99-149.50**	**<.001**
Antiarrhythmic	0.000	0.001	N.E.	N.E.	N.E.	N.E.	N.E.	N.E.
Sulfa drug	0.077	0.001	**7.00**	**1.60-22.60**	**<.001**	**4.83**	**1.09-21.54**	**<.001**
Antigout agent	0.027	0.001	**46.54**	**17.21-125.80**	**<.001**	**35.04**	**12.79-96.03**	**<.001**
Antibacterial	0.004	<0.001	**7.66**	**3.16-18.54**	**<.001**	**7.12**	**2.93-17.32**	**<.001**
NSAID	0.003	<0.001	**7.77**	**2.96-20.36**	**<.001**	**8.10**	**3.08-21.31**	**<.001**
Immune checkpoint inhibitor	0.258	0.001	**537.80**	**195.30-1481.00**	**<.001**	**486.70**	**175.70-1348.00**	**<.001**
Antifungal	0.012	0.001	**20.24**	**6.44-63.56**	**<.001**	**15.41**	**4.85-49.02**	**<.001**
Anti-peptic ulcer agent	0.006	<0.001	**13.72**	**5.79-2.51**	**<.001**	**14.69**	**6.17-35.02**	**<.001**
Mucolytic agent	0.002	0.001	**3.12**	**1.26-7.76**	**.014**	**2.83**	**1.13-7.07**	**.026**
Anti-cancer drug	0.031	0.001	**58.66**	**25.72-133.80**	**<.001**	**50.02**	**21.77-115.00**	**<.001**
Antipsychotic	0.007	<0.001	**15.83**	**6.71-37.35**	**<.001**	**13.66**	**5.61-33.25**	**<.001**
Insulin	0.040	0.001	**76.71**	**37.80-155.70**	**<.001**	**73.36**	**33.80-159.20**	**<.001**
Type-2 diabetes agent	0.010	0.001	**16.86**	**6.54-43.49**	**<.001**	**13.91**	**5.35-36.17**	**<.001**

Bold type indicates statistical significance.
CI, Confidence interval; *HR*, hazard ratio; *N.E.*, not evaluable; *NSAID*, nonsteroidal anti-inflammatory drug.

(Table II), which suggested a high risk of immune checkpoint inhibitor use. These agents abrogate regulatory immunity and augment antitumor immunity.[33-37] Therefore, these agents may promote SJS/TEN. Indeed, many cases of SJS/TEN in patients treated with immune checkpoint inhibitors have been reported previously.[15,38-41] Because the number of patients with cancer treated with immune checkpoint inhibitors has dramatically increased because of their remarkable efficacy, even at the advanced stage, physicians should be aware of the emergence of SJS/TEN.

We also showed that the administration of insulin and type 2 diabetes drugs was associated with a high risk of developing SJS/TEN, which should be interpreted carefully because we also detected type 2 diabetes as a risk. Whether having diabetes or using insulin and type 2 diabetes drugs is a risk of developing SJS/TEN, remains inconclusive, because this finding may be due to reverse causality. Alternatively, because insulin and type 2 diabetes drugs may be proxy variables for type 2 diabetes, this disease may be a potent risk factor for developing SJS/TEN.

Strengths and limitations

The strength of this study is the identification of risk factors and drugs that trigger the development of SJS/TEN using incidence-related information over a recent 7.5-year period. However, this study has several limitations. First, no genetic information was available for the individuals included in this study. Recent epidemiological studies have shown that several genetic factors specific to drugs have a risk of causing SJS/TEN.[42-44] Additionally, *in-silico* biomolecular studies of the distinctive combinations between human leukocyte antigen alleles and drugs have shown exquisite molecular interactions,[45-48] which are caused by the enhancement of cytotoxic T-cell reactions, such as allorecognition via the "pharmacological-interaction" concept.[47,49] Therefore, the diseases that were risk factors in our study might be associated with genetic factors, such as human leukocyte antigen alleles, predisposing to SJS/TEN. However, in the general population of this study, the probability that individuals had such genetic information is rare.

Second, information regarding the disease severity, skin histology of SJS/TEN, and the associated complications were unavailable. Third, all of the drugs and their interactions with the comorbidities that trigger SJS/TEN could not be examined in this study. To comprehensively search for drugs and the interactions that trigger SJS/TEN, high-throughput screening studies using the same method as that used in this study are required in the future. Fourth, because the database used in this study was based on National Health Insurance claim data in Shizuoka Prefecture, which does not cover health insurance claims of the Social Assurance Union, there is likely to have been selection bias. Fifth, over-the-counter drugs as causative drugs could not be assessed because the SKDB does not have claim data of such drugs. Nonsteroidal anti-inflammatory drugs

such as oxicam, which is strongly associated with SJS/TEN,[50] are not marketed as over-the-counter drugs, excluding topical piroxicam in Japan. Finally, the results may not apply to other ethnic groups because the present population was exclusively Japanese.

CONCLUSION

In a cohort population representing the general population, the risk factors for developing SJS/TEN were old age and a history of type 2 diabetes, peripheral vascular disease, and systemic autoimmune disease. Furthermore, in addition to previously reported drugs, the administration of immune checkpoint inhibitors, insulin, and type 2 diabetes drugs may trigger the development of SJS/TEN.

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Conflicts of interest

Nanako Ubukata is an employee of Sato Pharmaceutical Co, Ltd.

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