

ARTICLE

Real-world evidence of population differences in allopurinol-related severe cutaneous adverse reactions in East Asians: A population-based cohort study

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Abstract

Allopurinol-related severe cutaneous adverse reactions (SCARs) are strongly associated with *HLA-B*58:01*, the allele frequency (AF) of which is largely different among East Asians. However, evidence of population differences in SCAR development and relevance of genetic and/or other risk factors in the real-world remain unelucidated. This study aimed to evaluate population differences in allopurinol-related SCAR incidence related to genetic and/or other risk factors among East Asians in the real-world. A population-based cohort study was conducted using claims databases from Taiwan, Korea, and Japan. New users of allopurinol (311,846; 868,221; and 18,052 in Taiwan, Korea, and Japan, respectively) were followed up to 1 year. As control drugs, phenytoin and carbamazepine were used. The crude incidence rate ratios (IRRs) of SCARs for allopurinol against phenytoin or carbamazepine were the highest in Taiwan (IRR, 0.62 and 1.22; 95% confidence interval [CI], 0.54–0.72 and 1.01–1.47, respectively), followed by Korea (IRR, 0.34 and 0.82; 95% CI, 0.29–0.40 and 0.77–0.87), and the lowest in Japan (IRR, 0.04 and 0.16; 95% CI, 0.02–0.08 and 0.09–0.29). This order was accordant with that of AF ratios (AFRs) reported of *HLA-B*58:01* against alleles responsible for phenytoin- or carbamazepine-related SCARs. The IRRs were higher in patients with chronic kidney disease, females, and elderly. This study demonstrated population differences in the risk of allopurinol-related SCAR development among East Asians based

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on genetic and other common risk factors. This finding will help to promote appropriate risk management for allopurinol-related SCARs based on ethnic origins.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

Allopurinol-related severe cutaneous adverse reactions (SCARs) are strongly associated with *HLA-B*58:01*, the allele frequency of which is largely different among East Asians. However, there is no direct real-world evidence of population differences in SCAR development and the influence of genetic factors and/or other risk factors.

WHAT QUESTION DID THIS STUDY ADDRESS?

Do population differences in development of allopurinol-related SCARs, depending on genetic factors and/or other risk factors, exist among three East Asians in the real-world?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The current analysis, based on comparisons of relative risks of SCAR incidence, provides real-world evidence of population differences in allopurinol-related SCAR development risk among East Asians, which was consistent with differences in reported *HLA-B*58:01* frequencies, as well as identifying chronic kidney disease, female gender, and old age as common risk factors.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study helps to promote appropriate risk management strategies for allopurinol-related SCARs in the real-world considering risk factors based on the patients' ethnicity. Our approach is useful for evaluating population differences in the real-world.

INTRODUCTION

Ethnic or population differences in drug responses is a critical issue to consider in global drug development and postmarketing drug safety evaluation.^{1–3} The observed differences among populations or ethnicities reflect the overall intrinsic and extrinsic factors associated with ethnicity.⁴ Functional genetic polymorphisms are major intrinsic factors that may cause differences in drug response between ethnic groups. Knowledge of differences in allele frequencies (AFs) of functional genetic polymorphisms among different ethnic groups has been increasing, although the influence of genetic polymorphisms in real-world is not always considerable, or could be masked by other extrinsic factors.⁵ Leveraging the real-world data, including the ones from health insurance claims databases, has offered a key resource to promote efficient pharmacovigilance.^{6–8} Population-based claims databases have become available in drug safety research in East-Asian countries and collaborative research have been initiated.^{9–15} For facilitating appropriate planning of risk management strategy, it would be beneficial to demonstrate population differences in risk of adverse drug reactions (ADRs) and its dependency of functional genetic factors as well as other risk factors using real-world data. However, there have been very limited studies examining real-world evidence of population differences of ADRs.

Severe cutaneous adverse reactions (SCARs) to drugs, including Stevens–Johnson syndrome (SJS), toxic epidermal

necrosis (TEN), and drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS), are rare, but serious, potentially resulting in life-threatening, infectious, or chronic sequelae.^{16–20}

Allopurinol, an antigout agent, is one of the most frequent causes of SCARs in Asia and Europe.^{21–24} Previous studies indicated that the allele human leukocyte antigen (*HLA*)-*B*58:01* is a strong functional genetic factor for allopurinol-related SCARs in various populations.^{25–36} The AFs of *HLA-B*58:01* differed among populations of different ethnic origins¹ (e.g., relatively high in Chinese [0.101] and Koreans [0.061], but rare in Japanese [0.004], and Europeans [from 0.005 to 0.012]; Table S1), thus, those differences between East Asians are more than 25-fold. The incidence of allopurinol-induced SCARs was demonstrated to be reduced by prospective screening of the *HLA-B*58:01* allele in Chinese and Koreans.^{34–36} In contrast, although genetic polymorphisms associated with SCAR development by phenytoin (*CYP2C9*3*, *HLA-B*13:01*, *HLA-B*15:02*, and *HLA-B*51:01*)^{37,38} and carbamazepine (*HLA-B*15:02*, *HLA-B*15:11*, and *HLA-A*31:01*)^{33,38–41} have been identified, population differences in AFs of these genetic factors are very small among East Asians; less than twofold (Table S1).

In real-world scenarios, measuring ADR incidences can vary according to regionally different medical practices, including diagnostic criteria and coding rule as well as dosage, indication, and concomitant drugs. As for

allopurinol-related SCARs, although ethnic differences in AF of *HLA-B*58:01* have been recognized, evidence of population differences and the degree of influence of *HLA-B*58:01* or other risk factors in the real-world have not yet been investigated.

In this study, we conducted a multilateral collaborative cohort study under a common protocol to evaluate population differences in the incidence of allopurinol-related SCARs and possible relevance of genetic factors as well as other risk factors among East Asians by using claims databases from Taiwan, Korea, and Japan. For this purpose, we established a common protocol applicable to three claims databases, with the aim of minimizing potential regional differences, such as diagnostic coding rules, and evaluated the influence of genetic factors using literature-based information, while also considering the effects of control drugs.

METHODS

Data sources

We used three population-based health insurance claims databases—the National Health Insurance Research Database (NHIRD) in Taiwan, the Health Insurance Review and Assessment Service (HIRA) database in South Korea, and the Japan Medical Data Center (JMDC) insurance claims database in Japan. The NHIRD and HIRA databases cover the entire population, including ~ 23 million and 50 million persons, respectively, and are established from national insurance claims.^{8,9,42} The JMDC database is commercially available and provides claims data for patients with employer-based insurance that covers around 3 million persons. These databases have been used for collaborative research in Asia^{9–15} and studies on SCARs.^{24,25}

Study design

We developed a common protocol and conducted retrospective cohort studies by using the claims databases in Taiwan (from January 2010 to December 2015), Korea (from January 2009 to December 2016), and Japan (from January 2005 to September 2016). Based on our focus to determine the impact of genetic factors on population differences in SCAR development, we selected allopurinol as a target drug and phenytoin or carbamazepine as a control drug, although the indication of these control drugs—epilepsy and other psychoneurotic conditions—were different from that of allopurinol. The differences in AFs of functional genetic factors of phenytoin^{35,36} or carbamazepine^{31,37–39} for SCAR development (< 2-fold compared with Japan) are little or considerably smaller than those of

allopurinol (> 25-fold) among East Asians (see Table S1). By comparing with one of the negative control drugs regarding the AFs of functional genetic factors, we can eliminate the potential regional differences in the diagnostic criteria of SCARs and the way of coding among regions, although, basically, the diagnostic criteria of SCARs seem to be common in the three countries.^{17,33,43,44}

A base cohort was composed of new users of allopurinol, carbamazepine, or phenytoin. The cohort entry date was defined as the date of the first prescription of the target drug or the control drug (index date). We excluded patients whose record durations were less than 12 months before the entry date and those who were diagnosed with any SCAR (SJS, TEN, DIHS, or DRESS) before the index date.

Study patients were followed from their first prescription of any of the study drugs (allopurinol, phenytoin, or carbamazepine) until when the following events first occurred: the first hospitalization with the diagnosis of SCAR (SJS, TEN, DIHS, or DRESS); discontinuation of the study drug (gap period: 30 days after the expected end date of any prescription) or switch to another study drug; concomitant use of a study drug, or phenobarbital or zonisamide (an anti-epilepsy drug for which AFs of functional genetic factor for SCARs are different among East Asians); death; the day after 1 year from the index date; or the last day of the data collection period in each dataset.

Outcomes

The primary outcome was the first hospitalization with the diagnosis of SCAR (SJS, TEN, DIHS, or DRESS), for which a study drug was suspected to be a cause. We identified the incidence of SCAR based on the International Classification of Diseases, 9th revision clinical modification (ICD-9 CM) codes (695.1x or 693.0) in Taiwan or the International Classification of Diseases, 10th revision (ICD-10) codes (L51.1, L51.2, L51.3, or L27.0) in Korea and Japan. SCAR cases were considered as the outcome if a study drug was not prescribed following discharge. The secondary outcomes were the components of SCARs: one was the composite of SJS and TEN, whereas the other was DIHS/DRESS.

Confounding factors

In order to compare the characteristics of patients among the three countries, and to take into account the potential confounders and/or effect modifiers, we collected the following information: age at cohort entry; gender; year of cohort entry; comorbidities at 1-year baseline period before the index date, including skin disorders, allergic disease, liver disease, kidney disease, and malignant lymphoma (see Table S2); and

recent and concurrent use (within 1 month before or after the index date) of the major drugs that cause SCARs (see Table 1).

Evaluation of population differences

Relative risk measures, including crude incidence rate ratios (IRRs) and adjusted hazard ratios (HRs) of SCARs were used for the evaluation of population differences to counterbalance the potential regional differences in the diagnostic criteria of SCARs and the way of coding among regions, assuming that diagnostic criteria and coding rules of a target ADR are common for all drugs within each region. For the evaluation of relevance to genetic factors, IRRs or HRs were compared with literature-based values¹ of not only AFs but also AF ratios (AFRs) considering the potential impact of genetic polymorphisms associated with SCAR development by control drug, regarding the orders and magnitudes of differences. To investigate other nongenetic factors influencing the relative risk measures, we conducted secondary analyses stratified by patient characteristics.

Statistical analysis

We performed χ^2 tests and one-way analysis of variance to compare the baseline characteristics among regions. There were no missing values. Crude incidence rates (IRs) in users of each study drug were calculated using the person-year method separately for each country with their 95% confidence intervals (CIs). In the primary analyses, the crude IRRs (allopurinol vs. phenytoin, and allopurinol vs. carbamazepine) of SCARs with their CIs were calculated separately for each country based on the Poisson distribution. We also estimated the HRs of SCARs and 95% CIs by using a Cox proportional hazard model. Multivariable Cox proportional hazard model, including all potential confounders/effect modifiers listed in Table 1, was used to estimate the fully adjusted HRs and 95% CIs (see Code S1, Dataset format S1).

We conducted two secondary analyses on crude IRs and crude IRRs: first, stratified by age group, sex, baseline comorbidities, and concomitant drug use at baseline period to evaluate the contributions of risk factors other than the functional genetic factors; and second, stratified by initial dosage of the study drug to determine its influence on the estimates of IRR. We conducted all analyses using SAS version 9.4 (SAS Institute).

The study protocol was approved by the ethics committee of the National Cheng Kung University, National Seoul University, Tokyo University of Science, and National Institute of Health Sciences.

RESULTS

Study populations and patient characteristics

From the three databases, 311,846, 868,221, and 18,052 eligible new users of allopurinol; 88,534, 28,154, and 487 eligible new users of phenytoin; and 74,692, 763,624, and 6627 eligible new users of carbamazepine were identified in Taiwan, Korea, and Japan, respectively. Patient characteristics varied among the three study populations for each study drug (Table 1). Although the proportion of men was the highest in Japan for allopurinol and carbamazepine users, it was the highest in Korea for phenytoin users. The mean age of the Japanese cohort was the lowest for any study drug users because the JMDC database covers only beneficiaries of health insurance for employees and their family members under 75 years of age. The median of initial dosage was the lowest in Japan for any study drug. The prevalence of some concomitant drugs was very different among the regions. For comorbidities at baseline, the Korean and Taiwanese cohorts had the highest prevalence of allergic disease and chronic kidney disease (CKD), respectively, in all study-drug cohorts. For the allopurinol cohorts, the prevalence of skin disease and liver disease were highest in Korea and Japan, respectively.

Incidence rates and relative risks of SCARs

The number of cases of the first hospitalization with the diagnosis of SCARs within 1-year follow-up after the start of each study drug prescription is shown in Table S3. The average follow-up time (years) in Taiwan, Korea, and Japan was 0.73, 0.98, and 0.47 for allopurinol cohorts; 0.73, 0.87, and 0.30 for phenytoin cohorts; and 0.85, 0.98, and 0.33 for carbamazepine cohorts, respectively. The crude IRs of SCARs per 1000 person-years for allopurinol users were the highest in Taiwan (IR, 2.57; 95% CI, 2.37–2.79), followed by Korea (IR, 2.31; 95% CI, 2.30–2.31), and the lowest in Japan (IR, 2.00; 95% CI, 1.24–3.21). Regarding IRs for phenytoin and carbamazepine, the IRs were the highest in Japan, followed by Korea, and the lowest in Taiwan (Table S3).

The crude IRRs of SCARs for allopurinol users compared with phenytoin or carbamazepine users were the highest in Taiwan (IRR, 0.62 and 1.22; 95% CIs, 0.54–0.72 and 1.01–1.47, respectively), followed by Korea (IRR, 0.34 and 0.82; 95% CI, 0.29–0.40 and 0.77–0.87), and the lowest in Japan (IRR, 0.04 and 0.16; 95% CI, 0.02–0.08 and 0.09–0.29; Figure 1). The same trends as the IRR order were observed for the adjusted HRs of SCARs for allopurinol users against phenytoin or carbamazepine users (HR, 1.24 and 1.26, 95% CI, 1.04–1.50 and 1.01–1.56, respectively, in Taiwan; HR, 0.60 and 0.67, 95% CI, 0.59–0.61 and 0.67–0.68, respectively, in Korea; and HR, 0.13 and 0.22, 95% CI, 0.03–0.54 and 0.10–0.50, respectively, in Japan; Figure 1). These trends

TABLE 1 Characteristics of patients administered allopurinol/phenytoin/carbamazepine at the index date in the three East Asian populations

Drug	Items	Taiwan		Korea		Japan		p value*	
Allopurinol									
	Number of patients	311,846		868,221		18,052			
Sex	Male	237,985	76.3%	731,006	84.2%	16,987	94.1%	<0.001	
	Female	73,861	23.7%	137,215	15.8%	1065	5.9%		
Age; years	Mean (SD)	56.88	(16.8)	53.85	(16.2)	47.5	(11.4)	<0.001	
	Median (IQR)	57.0	(25.0)	54.0	(24.0)	48.0	(16.0)	ND	
	Age group							<0.001	
	0–9	542	0.17%	3324	0.38%	87	0.5%	<0.001	
	10–19	3238	1.04%	9412	1.08%	159	0.9%		
	20–29	13,983	4.48%	45,345	5.22%	829	4.6%		
	30–39	35,978	11.54%	116,75	13.43%	2999	16.6%		
	40–49	48,880	15.67%	167,273	19.27%	5866	32.5%		
	50–59	68,308	21.90%	203,284	23.41%	5489	30.4%		
	60–69	58,493	18.76%	157,809	18.18%	2289	12.7%		
	70–79	51,260	16.44%	122,924	14.16%	334	1.9%		
	>80	31,164	9.99%	42,275	4.87%	NA			
Initial dosage; mg/day	Mean (SD)	177.48	(223.8)	197.59	(84.1)	140	(71.0)	<0.001	
	Median (IQR)	100	(200.0)	200	(200.0)	100	(100.0)	ND	
Concomitant drugs	Drugs for acid-related disorders	166,503	53.4%	474,649	54.7%	7857	43.5%	<0.001	
	Diuretics	64,852	20.8%	135,531	15.6%	1294	7.2%	<0.001	
	Calcium channel blockers	90,425	29.0%	123,646	14.2%	3717	20.6%	<0.001	
	Corticosteroids for systemic use	79,176	25.4%	209,143	24.1%	2341	13.0%	<0.001	
	Antibacterials for systemic use	90,619	29.1%	234,110	27.0%	4017	22.3%	<0.001	
	Antimycobacterials	3315	1.1%	7891	0.9%	59	0.3%	<0.001	
	Immunosuppressants	3145	1.0%	8883	1.0%	135	0.7%	0.0012	
	Anti-inflammatory and antirheumatic products	221,435	71.0%	466,485	53.7%	7211	39.9%	<0.001	
	Antigout preparations	177,066	56.8%	12,563	1.4%	1575	8.7%	<0.001	
	Anaesthetics	3105	1.0%	3856	0.4%	2559	14.2%	<0.001	
	Analgetics	144,127	46.2%	161,798	18.6%	1778	9.8%	<0.001	
	Antiepileptics	16,582	5.3%	29,988	3.5%	353	2.0%	<0.001	
	Cough and cold preparations	102,594	32.9%	114,804	13.2%	2464	13.6%	<0.001	
	Ophthalmological drugs	51,301	16.5%	10,470	1.2%	1573	8.7%	<0.001	
	Medical history	Skin disease	93,528	30.0%	314,272	36.2%	3594	19.9%	<0.001
		Allergic disease	46,332	14.9%	260,705	30.0%	5091	28.2%	<0.001
Liver disease		46,935	15.1%	139,397	16.1%	6017	33.3%	<0.001	
Chronic kidney disease		66,768	21.4%	23,770	2.74%	374	2.1%	<0.001	
Malignant lymphoma		8425	2.7%	83,180	9.58%	796	4.4%	<0.001	

(Continues)

TABLE 1 (Continued)

Drug	Items	Taiwan		Korea		Japan		p value*	
Phenytoin									
	Number of patients	88,534		28,154		487			
	Oral alone/oral plus injection	45,764/42,770		15,767/12,387		246/241		<0.001	
Sex	Male	49,668	56.1%	16,891	60.0%	276	56.7%	<0.001	
	Female	36,866	41.6%	11,263	40.0%	211	43.3%		
Age, years	Mean (SD)	60.13	(19.1)	49.86	(29.4)	41.2	(17.2)	<0.0001	
	Median (IQR)	61.0	(28.0)	55	(35.0)	43.0	(27.0)	ND	
	Age group							<0.001	
	0–9	302	0.34%	4065	14.4%	15	3.1%	<0.001	
	10–19	1946	2.20%	1268	4.5%	50	10.3%		
	20–29	4228	4.78%	1146	4.1%	65	13.3%		
	30–39	6991	7.90%	1689	6.0%	80	16.4%		
	40–49	10,771	12.17%	3272	11.6%	100	20.5%		
	50–59	15,818	17.87%	4737	16.8%	97	19.9%		
	60–69	14,902	16.83%	4413	15.7%	66	13.6%		
	70–79	16,326	18.44%	5080	18.0%	14	2.9%		
	>80	15,250	17.23%	2484	8.8%	NA			
Initial dosage; mg/day	Mean (SD)	299.54	(712.4)	345.77	(204.8)	240	(253.0)	<0.001	
	Median (IQR)	300	(100.0)	250	(100.0)	200	(50.0)	ND	
Concomitant drugs	Drugs for acid-related disorders	62,117	70.16%	1514	5.38%	341	70.0%	<0.001	
	Diuretics	26,214	29.61%	504	1.79%	82	16.8%	<0.001	
	Calcium channel blockers	34,306	38.75%	336	1.19%	152	31.2%	<0.001	
	Corticosteroids for systemic use	31,955	36.09%	603	2.14%	156	32.0%	<0.001	
	Antibacterials for systemic use	53,102	59.98%	1474	5.24%	291	59.8%	<0.001	
	Antimycobacterials	935	1.06%	54	0.19%	1	0.2%	<0.001	
	Immunosuppressants	959	1.08%	100	0.36%	5	1.0%	<0.001	
	Anti-inflammatory and antirheumatic products	50,341	56.86%	662	2.35%	249	51.1%	<0.001	
	Antigout preparations	6564	7.41%	2163	7.68%	6	1.2%	<0.001	
	Anaesthetics	8504	9.61%	2	0.01%	273	56.1%	<0.001	
	Analgetics	62,400	70.48%	498	1.77%	229	47.0%	<0.001	
	Antiepileptics	31,797	35.92%	348	1.24%	275	56.5%	<0.001	
	Cough and cold preparations	46,695	52.74%	566	2.01%	128	26.3%	<0.001	
	Ophthalmological drugs	22,144	25.01%	216	0.77%	111	22.8%	<0.001	
	Medical history	Skin disease	27,056	30.56%	9938	35.3%	163	33.5%	<0.001
		Allergic disease	12,967	14.65%	12,410	44.1%	145	29.8%	<0.001
Liver disease		11,922	13.47%	7585	26.9%	110	22.6%	<0.001	
Chronic kidney disease		13853	15.6%	1205	4.3%	3	0.6%	<0.001	
Malignant lymphoma		783	0.88%	1179	4.19%	36	7.4%	<0.001	

(Continues)

TABLE 1 (Continued)

Drug	Items	Taiwan		Korea		Japan		p value*	
Carbamazepine									
	Number of patients	74,692		763,624		6627			
Sex	Male	32,493	43.5%	319,643	41.9%	3356	50.6%	<0.001	
	Female	42,199	56.5%	443,981	58.1%	3271	49.4%		
Age; years	Mean (SD)	57.24	(16.8)	54.92	(16.5)	35.0	(19.5)	<0.001	
	Median (IQR)	58.0	(23.0)	56	(24.0)	38.0	(32.0)	ND	
	Age group							<0.001	
	0–9	243	0.33%	1617	0.21%	1057	15.9%		
	10–19	1341	1.80%	15,994	2.09%	683	10.3%		
	20–29	3240	4.34%	44,226	5.79%	606	9.1%		
	30–39	6461	8.65%	79,224	10.37%	1104	16.7%		
	40–49	11,094	14.85%	126,656	16.59%	1450	21.9%		
	50–59	17,439	23.35%	181,698	23.79%	1132	17.1%		
	60–69	15,470	20.71%	151,001	19.77%	468	7.1%		
	70–79	13,039	17.46%	125,585	16.45%	127	1.9%		
	>80	6365	8.52%	37,623	4.93%	NA			
Initial dosage; mg/day	Mean (SD)	282.79	(260.4)	385.66	(127.7)	228	(280.0)	<0.001	
	Median (IQR)	200	(200.0)	400	(200.0)	200	(100.0)	ND	
Concomitant drugs	Drugs for acid-related disorders	43,359	58.1%	15,433	2.02%	2700	40.7%	<0.001	
	Diuretics	8323	11.1%	5091	0.67%	149	2.2%	<0.001	
	Calcium channel blockers	16,939	22.7%	4244	0.56%	463	7.0%	<0.001	
	Corticosteroids for systemic use	18,439	24.7%	6384	0.84%	1125	17.0%	<0.001	
	Antibacterials for systemic use	24,656	33.0%	8006	1.05%	2489	37.6%	<0.001	
	Antimycobacterials	220	0.3%	327	0.04%	1	0.0%	<0.001	
	Immunosuppressants	507	0.7%	269	0.04%	27	0.4%	<0.001	
	Anti-inflammatory and antirheumatic products	55,784	74.7%	13,852	1.81%	2459	37.1%	<0.001	
	Antigout preparations	4347	5.8%	23,583	3.09%	29	0.4%	<0.001	
	Anaesthetics	523	0.7%	162	0.02%	1040	15.7%	<0.001	
	Analgetics	46,533	62.3%	6271	0.82%	1864	28.1%	<0.001	
	Antiepileptics	16,675	22.3%	3175	0.42%	1936	29.2%	<0.001	
	Cough and cold preparations	28,342	37.9%	4410	0.58%	1967	29.7%	<0.001	
	Ophthalmological drugs	16,844	22.6%	424	0.06%	1056	15.9%	<0.001	
	Medical history	Skin disease	27,879	37.3%	327,027	42.8%	2512	37.9%	<0.001
		Allergic disease	14,313	19.2%	411,938	53.9%	3180	48.0%	<0.001
Liver disease		9127	12.2%	162,854	21.3%	1472	22.2%	<0.001	
Chronic kidney disease		6835	9.2%	16,231	2.1%	28	0.4%	<0.001	
Malignant lymphoma		247	0.3%	1432	0.2%	129	1.9%	<0.001	

SD, standard deviation; IQR, interquartile range; NA, not available; ND, not determined

*Regional difference was evaluated using chi-square test or one-way analysis of variance.

of relative risk measures among regions were in accordance with the order of the previously reported frequencies of the allele responsible for allopurinol-related SCARs—*HLA-B*58:01*—0.101, 0.061, and 0.004, respectively (Table S1).

The orders of IRRs and HRs also accorded with the AFRs of *HLA-B*58:01* to alleles responsible for phenytoin-related SCARs or to those for carbamazepine-related SCARs (Table S1).

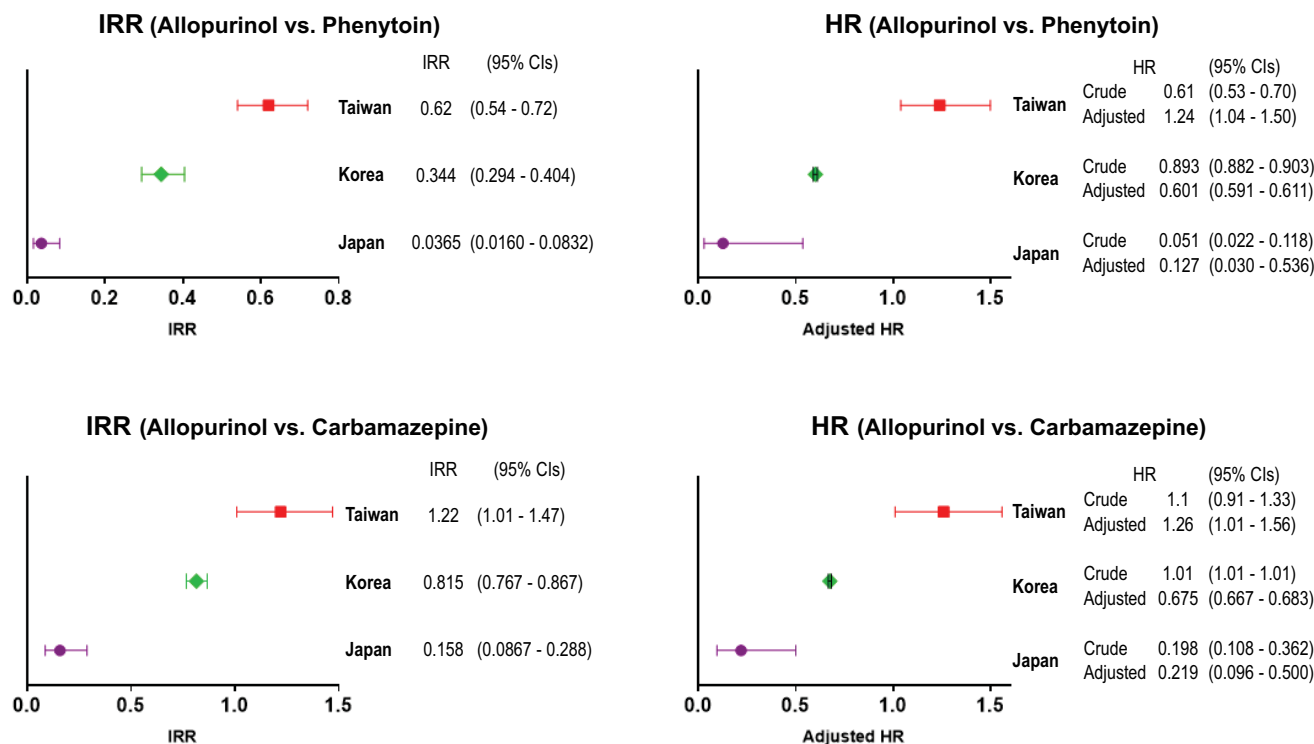


FIGURE 1 Comparison of incidence rate ratios and hazard ratios of allopurinol-related SCARs among the three East Asian populations. CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; SCARs, severe cutaneous adverse reactions

Secondary analyses

For secondary outcomes, the majority of cases were diagnosed as DIHS/DRESS in Korea and Japan for all the three study drugs, whereas the proportion of SJS/TEN against DIHS/DRESS cases was relatively higher in Taiwan than in the other two regions, especially for carbamazepine (Table S5). The crude IRs of SJS/TEN were the highest in Taiwan, followed by Korea, and the lowest in Japan in allopurinol and phenytoin users (Table S5). The crude IRRs of SJS/TEN were higher in Korea and Taiwan than in Japan when allopurinol was compared with either phenytoin or carbamazepine, and the IRRs of DIHS/DRESS were the highest in Taiwan, followed by Korea, and the lowest in Japan in both comparisons (Table S6).

The results of analyses stratified by possible effect modifier/confounder showed that in allopurinol users, the IRs as well as IRRs of SCARs were commonly higher in female patients and in patients with CKD in all the three populations (Table S4 and Figure 2). Furthermore, relatively higher IRs for allopurinol users and the IRRs in younger patients (< 9-years-old) were observed in Taiwan and Korea, but no SCAR cases were found in Japan. In elderly patients (≥ 70 -years-old), higher IRs and IRRs were commonly observed among all three populations (Table S4 and Figure 3). The order of IRRs (Taiwan > Korea > Japan) was almost similar to the results of primary analyses for any stratified groups. Although the IRs in users of allopurinol and concomitant drug(s) were higher than those

of nonusers of concomitant drug(s) for acid-related disorders, diuretics/calcium channel blockers, antibacterials for systemic use /antimycobacterials, and anti-epileptics drugs, no apparent differences of IRRs were noted for any drug classes except for diuretics/calcium channel blockers. Among the three populations, the IRRs were the highest in Korea in concomitant drug users for many of the drug classes (data not shown).

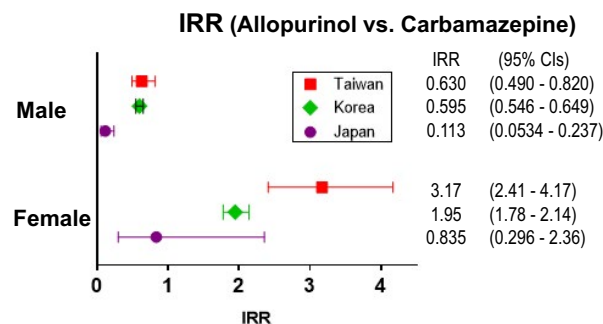
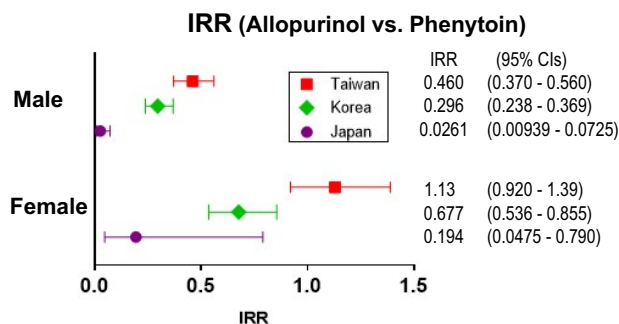
The event rates and relative risks stratified by initial dosage of the study drug are shown in Tables S7 and S8. The IRs did not clearly differ by initial dosage except for phenytoin in Taiwan. Although the IRRs were lower in the higher dosage group except in Japan, the order was consistently the highest in Taiwan, followed by Korea, and the lowest in Japan in each stratified group.

DISCUSSION

Contribution of genetic factors and other risk factors to allopurinol-related SCARs

In the real-world, factors potentially influencing allopurinol-related SCARs include not only genetic polymorphisms but also other intrinsic and extrinsic factors, which could vary considerably across regions. To the best of our knowledge, this is the first study that demonstrated a population differences among East Asians in the incidence of

(a) Sex



(b) Chronic kidney disease

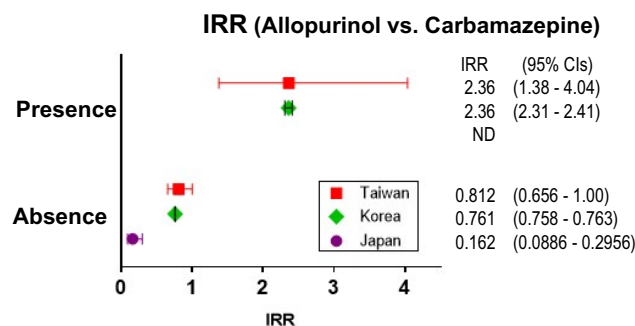
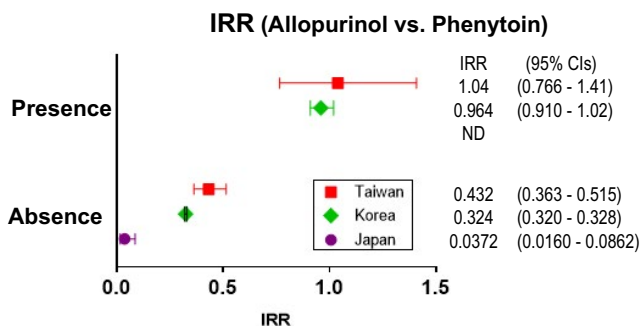


FIGURE 2 Comparison of incidence rate ratios of allopurinol-related SCARs among the three East Asian populations stratified by sex and chronic kidney disease. CI, confidence interval; IRR, incidence rate ratio; ND, not determined; SCARs, severe cutaneous adverse reactions

allopurinol-related SCARs in the setting of daily clinical practice by using claims databases. The trends in both of the crude IRRs and HRs of SCARs for allopurinol users compared with those of phenytoin or carbamazepine among three countries (Taiwan > Korea > Japan), with a considerably larger difference between Japan and the two other countries (Figure 1), were in accordance with the order of the AFR of *HLA-B*58:01* to responsible alleles for SCARs by a control drug (allopurinol/phenytoin or allopurinol/carbamazepine; Table S1). These findings support our hypothesis that the differences in genetic factors could contribute to the integrated population differences in the risk of allopurinol-related SCAR development among the three East Asian populations. Clinical application of genetic testing of *HLA-B*58:01* before allopurinol therapy was limited because this HLA test had not been covered by the National Health Insurance in all countries. We found that the implementation rate of *HLA-B*15:02* testing for carbamazepine therapy, which was available for health insurance in Taiwan since June 2010, was also very low (5%). Thus, the impact of genetic testing was negligible in this study (Table S1).

Although the proportion of SJS/TEN cases against that of DIHS/DRESS cases varied among regions (Table S5), the order of crude IRRs (Taiwan > Korea > Japan) was consistent for DHIS/DRESS. Because the diagnosis criteria adopted in each country originated from the same criteria,^{17,33,43,44} the higher proportion of SJS/TEN versus DIHS/DRESS in

Taiwan (Table S5) might be attributed to the region-specific practice of disease recording. Because patients with SJS/TEN are usually treated in intensive care unit (ICU) in Taiwan, we repeated the primary analyses using a modified SCAR definition, including ICU treatment. The result revealed that IR values decreased, but the IRR (allopurinol/phenytoin [A/P]) and IRR (allopurinol/carbamazepine [A/C]) for SCARs obtained using the modified definition were similar to those obtained using the original definition (data not shown). Thus, even a possible regional difference in disease recording might not influence our evaluation approach of population differences by using IRR.

This study indicated that CKD, being female, and elderly patients could be at risk for allopurinol-related SCARs in all three populations. We found that CKD had much higher, smaller, and little impact on the IRs of SCARs by allopurinol, phenytoin, and carbamazepine, respectively. This finding is also consistent with those from studies showing that CKD is a risk factor for allopurinol-related SCARs.^{25,36} Because renal function is known to be lower in elderly and female individuals, these factors would be related. Notably, the order of IRRs (A/P and A/C) for the three populations in each stratified group (i.e., males, females, CKD presence, CKD absence, and each age group) was mostly constant (Taiwan > Korea > Japan; Figures 2, 3), and thus, this trend was consistent with the order of AFRs. This finding indicates that age, gender, and renal function together with *HLA-B*58:01* may modulate the

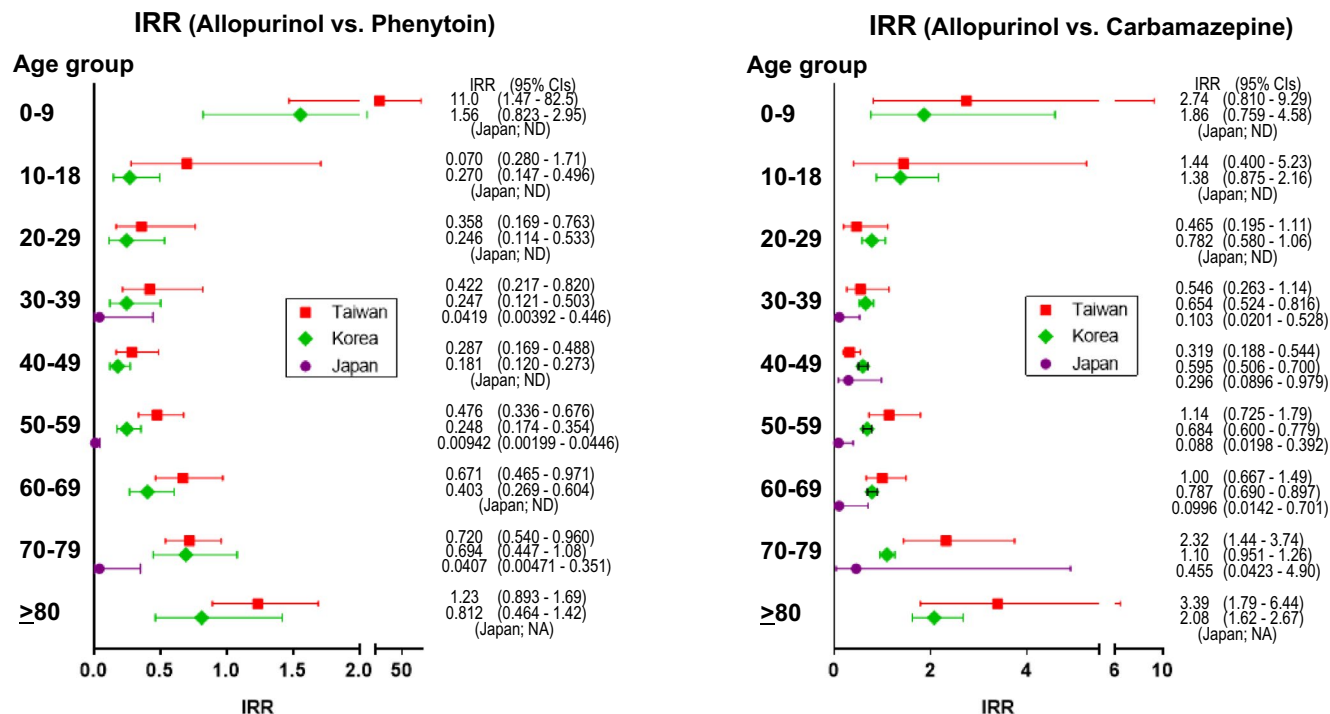


FIGURE 3 Comparison of incidence rate ratios of allopurinol-related SCARs among the three East Asian populations stratified by age group. CI, confidence interval; IRR, incidence rate ratio; ND, not determined; NA, not available; SCARs, severe cutaneous adverse reactions

incidence of allopurinol-related SCARs in addition to genetic factors.

Although the proportion of concomitant drug users for phenytoin and carbamazepine was lower in the Korean population and the IRs of phenytoin- and carbamazepine-related SCARs were lower in the concomitant-drug user group in Korea (data not shown), the order of HRs (A/P and A/C) which adjusted for concomitant drugs among regions was consistent with that of crude IRRs. This finding suggests that regional difference in concomitant drug usage with antiepileptic agents might not have a significant impact on population differences of SCAR risk.

Although the initial dosages of the three study drugs were different among the regions, the order of IRRs among regions was constant for each stratified group (Table S8), in accordance with the order of AFRs (Table S1). Furthermore, IRRs of the higher dosage groups in Japan (for whole dosage or >median) were lower than those of the lower dosage groups of Taiwan and Korea. Thus, different initial dosages among countries may not affect the current evaluation results based on IRR comparison.

The Japanese cohort was younger than other two cohorts because patients older than 75 years were not included in the database; hence, we conducted an ad hoc analysis to determine the possible impact of the difference of age distribution among the three study populations. We estimated the age-adjusted (standardized) IRs of SCARs for Korean and Taiwanese cohorts by applying age-group distribution of Japanese cohort as the standard population. Although the IRs

for Korean and Taiwanese cohorts were lower than those in the primary analysis, we confirmed that the trend of the IRRs (A/P and A/C) was the same as in the primary analysis (i.e., Taiwan > Korea > Japan; data not shown).

Strengths and limitations of this study

The primary strength of our study is the cohort design using population-based databases, including two national databases covering the entire population in Taiwan and South Korea, which ensures the generalizability of our results. Although the proportion of elderly patients was small in the Japanese database, the general population setting can reflect routine medical practice.

This study has several limitations. First, our SCAR definition based on claims has not been validated. However, we restricted the SCAR definition only to hospitalized cases with discontinuation of the study drug to reduce misclassification bias for relative risk measures. Second, regional differences might exist in the diagnosis or coding criteria (ICD-9 in Taiwan or ICD-10 codes in Korea and Japan). Third, information for other potential confounders/effect modifiers was not available in this study. To eliminate these limitations, we performed the analysis using relative risk measures (IRRs and HRs) against a reference drug and compared the order or degree of relative risks among populations to evaluate population differences in allopurinol-related SCAR development. This approach can also serve our primary purpose, to clarify the relevance of genetic

factors as well as to explore other potential factors. Another limitation is the selection of functional genetic factors and assumption of these additive effects. We used the AFs calculated based on a literature review (Table S1), considering that there are no global standards. There may be other functional genetic factors, the clinical significance of which has not yet been established. However, based on what is currently known, we assume that the selected genetic factors are the most representative and high-priority ones associated with SCARs by the target and control drugs, for which the differences/similarities in AFs are evident.

Last, a small number for the Japanese population could have introduced bias. However, our data on carbamazepine-related SCAR incidence (0.4%: 28 cases/6627 patients) is consistent with historical data (0.3%: 4 cases/1312 patients registered in Biobank, Japan), with SCAR diagnosed by physicians.⁴¹ With regard to the phenytoin cohort, the number of patients is much smaller than that in other cohorts. However, the 95% CIs of IRR (A/P) and HR (A/P) in Japan did not overlap with those in Taiwan and Korea, indicating considerable differences between Japan and other countries. In addition, we investigated the number of spontaneous reports of SCARs in Japan in 2005–2016 using VigiBase, a database recording ADRs reported to the World Health Organization, and calculated the relative number of SCAR reports to the number of subjects in each cohort (Table 1) and compared them among study drugs. The results indicated that the relative number of allopurinol-related SCAR reports were much less than that of phenytoin-related SCAR reports (data not shown). Consequently, the findings of the present study are reasonable.

Meaning of the study

Overall, this study has provided clinically and regulatory important suggestions. First, this study demonstrated real-world evidence of ethnic differences in allopurinol-related SCARs among East Asians, which are possibly related to ethnic differences in the responsible genetic factor, as well as other common risk factor. Furthermore, this finding would provide insights into the risk management strategy to minimize the incidence of SCAR. This might promote global drug development and/or international pharmacovigilance while taking into account risk populations with specific genetic polymorphisms and other common risk factors, as well as facilitate the development of domestic risk management strategy (i.e., selection of the right medication for individual patients in clinical practice by considering the risk factors based on their ethnicity). In addition, our approach based on a common protocol applicable to claims databases in different regions could facilitate research on other drugs to evaluate population differences and intrinsic and extrinsic factors in the real-world.

CONCLUSIONS

This study demonstrated the population differences in allopurinol-related SCAR development in East Asians in the real-world setting. The observed population differences were related to the differences in the reported AFs of responsible genetic polymorphisms, in addition to other common risk factors such as CKD, female gender, and advanced age. These findings provide important insights into appropriate risk management strategies while considering the risk factors based on the patients' ethnicity. However, the size of population remains limited, especially for Japan, and thus further studies with larger population sample is warranted.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

T.S. and K.S. wrote the manuscript. T.S., K.S., and Y.S. designed the research. T.S., C.C., H.P., Y.K., M.Y., M.F., Y.K., M.T., Y.S., and K.S. performed the research. T.S., C.C., H.P., and M.F. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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