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RESEARCH ARTICLE

Epidemiology of drug hypersensitivity reactions using 6-year national health insurance claim data from Korea

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Abstract

Background Drug hypersensitivity reactions (DHRs) constitute a large portion of adverse drug reactions (ADRs), but studies for DHR incidence based on national data are scarce. *Objective* This study aimed to estimate the incidence and patterns of DHRs in a Korean population and the associated utilization of medical resources using the national claims data. *Setting* The retrospective cohort study performed using the national insurance claim database of the Health Insurance Review and Assessment (HIRA) in Korea. *Methods* The International Classification of Disease 10th revision code was used to identify DHRs with 20 drug induced DHR codes. The claim data with a diagnosis of DHR in the 2009-2014 periods were analyzed. *Main outcome and measure* The annual incidence and the 6-year incidence rates were calculated. Incidence rate coefficients were analyzed by sex, age, and year. DHRs following with visits of emergency department (ED) or intensive care unit (ICU) were assessed for utilization of medical resources and risk of ER or ICU visits by sex and age *Results* A total of 535,049 patients with 1,083,507 claims were assessed in the HIRA database for 6 years. DHR incidence was high in the elderly. The risk of ED and ICU visit with DHR was also higher in the elderly than in the young [highest relative risk, RR of ED 2.59 (1.65–4.07), ICU 5.04 (2.50–10.18)]. DHRs related to blood were high in the young age. *Conclusion* Incidence of DHRs in the real-world clinical practice was higher in the elderly and female. Clinical consequence was more severe in the elderly.

Keywords Adverse drug reactions (ADRs) · Drug hypersensitivity · Health insurance database · Incidence · Korea

Impacts on practice

- Drug-induced dermatitis, allergic purpura, and toxic liver disease are the DHRs with the most frequent incidence in Korea, and the most severe DHRs are the shock due to anesthesia and toxic epidermal necrolysis (TEN).
- Medical staff should be suspicious of the possibility of DHRs, especially in elderly.

Introduction

Drug therapy is often accompanied by unexpected, unwanted reactions to patient with adverse drug reactions (ADRs). ADRs accounted for 3–6% of all hospitalizations, and as many as 10–15% inpatients experienced ADRs [1–3]. There are two subtypes of ADRs: Type A reactions are dose dependent and predictable, while type B reactions are dose independent and unpredictable [4]. Drug hypersensitivity reactions (DHRs) are an example of type B reactions. The

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term 'drug allergy' is often used in a general sense; however, it should only be used for an ADR with established immunological mechanisms. DHR is, therefore, considered the preferred term and includes both allergic and non-allergic reactions [5, 6].

Many studies have demonstrated the importance and severity of DHRs, which constitute one-third of all ADRs. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been related to a high risk of morbidity and mortality [7]. In a retrospective study of 63 hospitals in the USA, 33.5% of ADRs with emergency department (ED) visits were associated with DHRs [8]. The epidemiologic data related to DHRs have increased steadily. The general clinical symptoms, culprit drugs, and incidence of DHRs have been reported [9, 10]. However, nationwide general population cohort studies with various DHRs are few.

Korea has begun to collect the self-reporting ADRs by patient through the designated institutions in 1988. The regional pharmacovigilance (PV) centers were reorganized in 2006, and Korea Institute of Drug Safety and Risk Management (KIDS) was established for the purpose of centralized systematic ADR data management in 2012. Currently, patients or health care provider reports ADRs voluntarily via 27 regional PV centers and KIDS.

The Korean national health insurance (NHI) system for all citizens has implemented with the electronic claim process through the Health Insurance Review and Assessment (HIRA). The system includes an administrative claims database that can be effectively utilized for epidemiological research [11–13]. HIRA database would be useful to carry out the epidemiology study of DHR since the DHR cohort studies are very few for the rare and unexpected events.

Aim of the study

Studies for DHR incidence based on national data are scarce. This study aimed to estimate the incidence and patterns of DHRs in a Korean population and the associated utilization of medical resources related to DHRs using the national claims data.

Ethics approval

This study was approved by Institutional Review board (IRB) at Ajou University (No. 201507-HR-BM-001-01). The study also obtained an official approval from the HIRA research inquiry commission. Each patient's personal privacy was protected by de-identification of the national insurance claim data for analysis.

Table 1 Diagnostic codes of DHRs selected for the study

ICD-10 code	Description
D59.0	Drug-induced autoimmune hemolytic anemia (DIHA)
D59.2	Drug-induced non-autoimmune hemolytic anemia
D61.1	Drug-induced aplastic anemia
D69.0	Allergic purpura
D69.5	Secondary thrombocytopenia
J70.2	Acute drug-induced interstitial lung disorders
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K85.3	Drug-induced acute pancreatitis
L10.5	Drug-induced pemphigus
L23.3	Allergic contact dermatitis (ACD) due to drugs in contact with skin
L25.1	Unspecified contact dermatitis due to drugs in contact with skin
L27.0	Generalized skin eruption due to drugs and medicaments
L27.1	Localized skin eruption due to drugs and medicaments
L51.1	Stevens–Johnson syndrome (SJS)
L51.2	Toxic epidermal necrolysis (TEN)
L56.1	Drug photoallergic response
M32.0	Drug-induced systemic lupus erythematosus (SLE)
R50.2	Drug-induced fever (DIF)
T88.2	Shock due to anesthesia
T88.6	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered

DHRs drug hypersensitivity reactions, *ICD-10* the International Classification of Disease 10th revision

Table 2 Sex- and age-wise distribution of patients with DHRs and the number of claims each year

		Year											
		2009		2010		2011		2012		2013		2014	
Patients (n)	Total		93,371		90,045		90,155		88,060		87,140		86,278
Sex (n)	Male		39,637		37,906		38,127		37,630		37,148		36,814
	Female		53,734		52,139		52,028		50,430		49,992		49,464
Age (years, n)													
≤ 19	< 5	16,581	3864	15,090	3920	15,288	4234	13,912	3798	13,864	3454	13,268	3238
	5–9		4709		4023		4188		3964		4155		3950
	10–14		3647		3109		3014		2640		2679		2567
	15–19		4361		4038		3852		3510		3576		3513
20–44	20–24	32,443	4602	29,728	4286	28,706	4277	26,985	4100	26,059	4251	25,182	4238
	25–29		6897		6058		5532		4921		4516		4403
	30–34		6280		5854		5896		5673		5449		5309
	35–39		7252		6589		6064		5577		5353		5129
	40–44		7412		6941		6937		6714		6490		6103
45–64	45–49	29,594	8472	29,889	8093	30,393	7734	30,453	7398	30,230	6981	29,976	6873
	50–54		8618		8693		9001		9134		8925		8545
	55–59		6671		7023		7452		7819		8050		8262
	60–64		5833		6080		6206		6102		6274		6296
≥ 65	65–69	14,753	5822	15,338	5829	15,768	5744	16,710	5790	16,987	5662	17,852	5839
	70–74		4585		4852		5009		5254		5447		5519
	75–79		2621		2889		3119		3500		3515		3882
	80–84		1221		1263		1315		1529		1663		1793
	> 84		504		505		581		637		700		819
Total claims (n)			176,346		169,199		176,342		189,073		187,623		184,924

DHRs drug hypersensitivity reactions

Methods

Definition of DHRs

In this retrospective cohort study, we used the International Classification of Disease 10th revision (ICD-10) codes to define DHRs. Stausberg and Hasford [14, 15] classified DHRs into seven diagnostic code categories in accordance with their validity as indicators for ADRs. The most relevant category was level A with subgroups of A1 and A2. A1 was defined as 'caused by a drug,' and A2 was defined as 'caused by a drug or other substance'. Benkhaial et al. [16] specified the codes of allergic drug reaction that were potentially drug-induced. Ten DHR diagnostic codes from the study by Stausberg et al. and those specified by Benkhaial et al. were selected to identify DHRs with level A category. Total 20 DHR codes were included for the final analysis (Table 1).

Data source and statistical analysis

The Korean national insurance claim data from HIRA were reviewed for the period of 2009–2014. The NHI is a universal health care system that covers the entire Korean population of approximately 50 million as a social insurance benefits scheme. The HIRA data consist of demographic information, diagnosis by the Korean Standard Classification of Disease-6 (KCD-6) with extension of ICD-10, prescription records, medical procedures and services, health care providers, and medical resources utilization. To analyze the incidence of DHRs among all Korean, the data for total population enrolled in the NHI were referred to through the open access data available from the Korean Statistical Information Service (KOSIS) (www.kosis.kr).

Incidence trends were analyzed for each DHR code. The annual incidence proportion (IP) for years from 2009 to 2014 was calculated as the number of patients with each DHR code divided by the total number of insured persons. For example, the number of patients with 'D59.0' (drug-induced autoimmune hemolytic anemia, DIHA) was 119 and the total number of insured persons in 2009 was 48,613,534; the annual IP of 'D59.0' in 2009 is 0.0000024 (24/10 million persons). The incidence rates (IRs) during the 6-year period were calculated based on person-years. The number of patients with each DHR code was divided by disease-free years of total insured persons. While the number of patients with D59.0 in year 2009–2014 was total 441 (119,

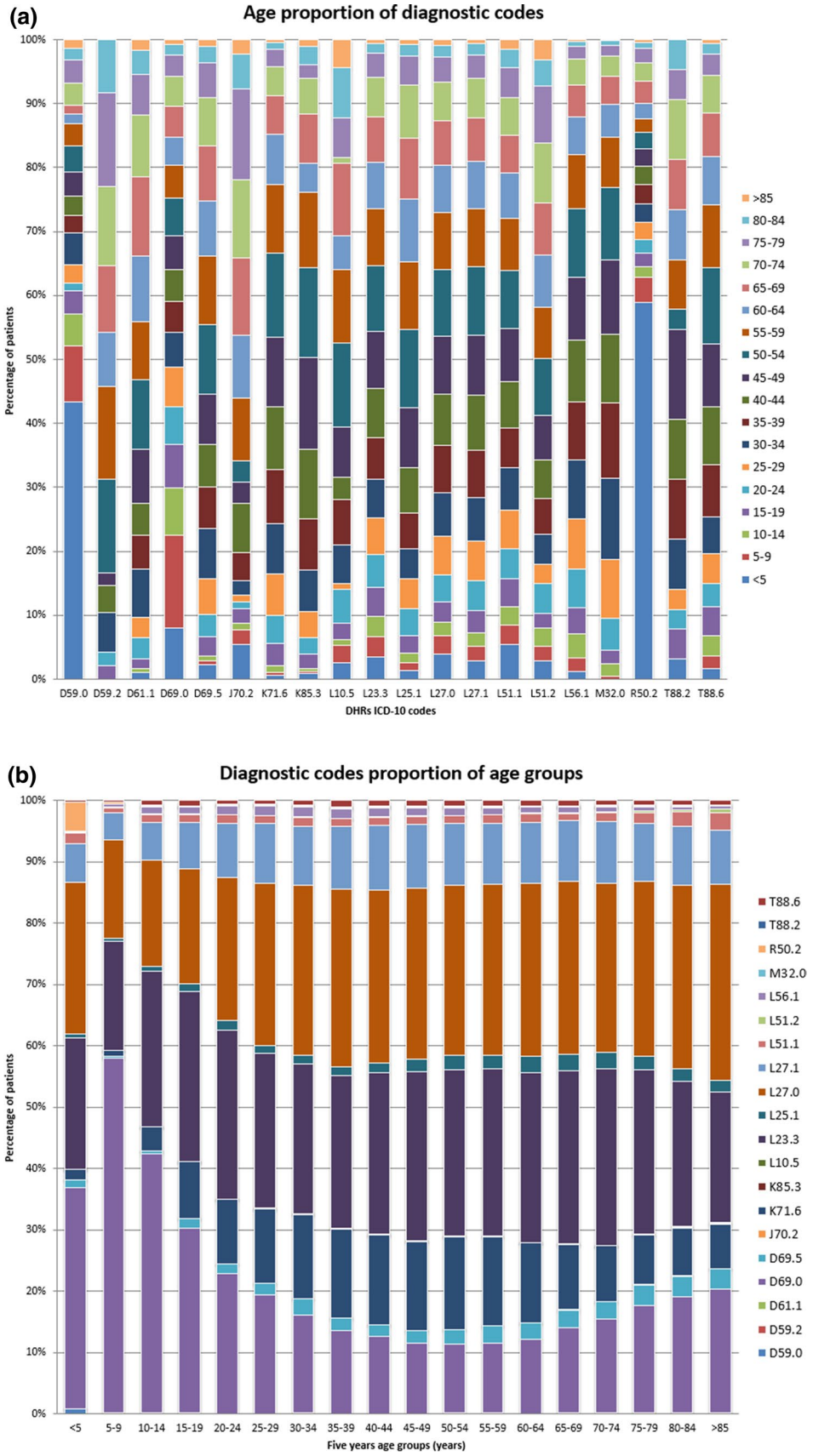

Fig. 1 Distribution of age and DHR diagnostic codes represented by 100% stacked column graphs. **a** Age proportion for DHR diagnostic codes and **b** DHR diagnostic codes proportion for age groups

Table 3 Incidence of drug hypersensitivity reaction (DHR codes)

ICD-10 code	Incidence proportion, per 10MP (n)						Six-year incidence rate, per 10MPY (2009–2014)	
	2009	2010	2011	2012	2013	2014	Crude rates	ASRs
D59.0	24	36	11	6	5	7	15	21
D59.2	2	1	2	1	1	2	2	1
D61.1	11	12	3	5	4	3	6	5
D69.0	3407	3200	3455	3404	3400	3465	3389	3882
D69.5	306	368	393	429	438	418	393	332
J70.2	3	3	2	3	3	3	3	3
K71.6	2048	2061	2025	2024	2037	2080	2046	1709
K85.3	18	18	22	20	20	20	20	16
L10.5	6	4	4	3	2	4	4	3
L23.3	5426	5276	4908	4266	4310	4060	4701	4320
L25.1	456	341	349	300	270	244	326	273
L27.0	4930	4731	4811	4923	4624	4447	4743	4295
L27.1	1827	1694	1620	1674	1639	1634	1681	1495
L51.1	242	204	225	226	273	283	243	228
L51.2	22	17	22	27	25	23	23	20
L56.1	232	204	167	192	169	227	198	179
M32.0	28	28	26	23	19	21	24	21
R50.2	39	47	100	67	46	57	59	91
T88.2	2	3	2	1	3	2	2	2
T88.6	178	161	139	139	143	148	151	132

DHR drug hypersensitivity reaction, *ICD-10* the International Classification of Disease 10th revision, *ASRs* age-standardized rates, *10MP* 10 million persons, *10MPY* 10 million person-years

177, 55, 29, 27, and 34 for each year), the disease-free year of 119 patients in 2009 was approximately 1 year and that of 177 patients in 2010 was approximately 2 years. The total number of insured persons in 6 years calculated by dynamic population method was 49,464,599 [17]. In such a case, the IR of D59.0 is calculated as: $(119+177+55+29+27+34)/[(119*1)+(177*2)+(55*3)+(29*4)+(27*5)+(34*6)+((49{,}464{,}599-441)*6)]=0.0000015$ (15/10 million person-years).

The IRs were expressed as both crude rates and age-standardized rates (ASRs). The world standard population distribution from the WHO was used to calculate the ASRs. IP and IR for each DHR were presented as 10 million persons (10MP) and 10 million person-years (10MPY), respectively. Poisson regression analysis was performed to analyze the IR coefficient by sex, age, and year. The number and cost of DHR-related ED and intensive care unit (ICU) visits were also assessed. Odds ratio (OR) among DHR codes about ED and ICU visits and the relative risk (RR) of each codes about ED and ICU visits by sex and age were calculated. Chi-square test and Fisher's exact test were used in comparing categorical data.

Statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). IR coefficients, OR and RR were presented with 95% confidence intervals (CIs) and p values less than 0.05 were considered significant.

Results

Total number of claim data with DHR codes was 1,083,507 in 535,049 patients during the period of 2009–2014. Female were 57.5% of patients. The highest proportion of DHRs was observed in the 45–64 years group. DHRs decreased in the young ≤ 19 years and increased continuously in the elderly ≥ 65 years on reflection of the age distribution in Korean population (Table 2). Patients with diagnosis of DIHA (D59.0) and drug-induced fever (DIF) (R50.2) were concentrated in the less than 5 years group (43.31 and 58.84%, respectively). The ICD-10 codes for diseases associated with blood occurred in the young age group (0–19 years, 33.64%) at a higher incidence. The codes for diseases of the skin and subcutaneous tissue were higher in the adults (87.32%) compared to the younger (12.68%) (Fig. 1).

The DHRs with a crude incidence rate (IR) of more than 2000 patients per 10MPY were allergic contact dermatitis (ACD) (L23.3, 4701/10MPY), generalized skin eruption (L27.0, 4743/10MPY), allergic purpura (D69.0,

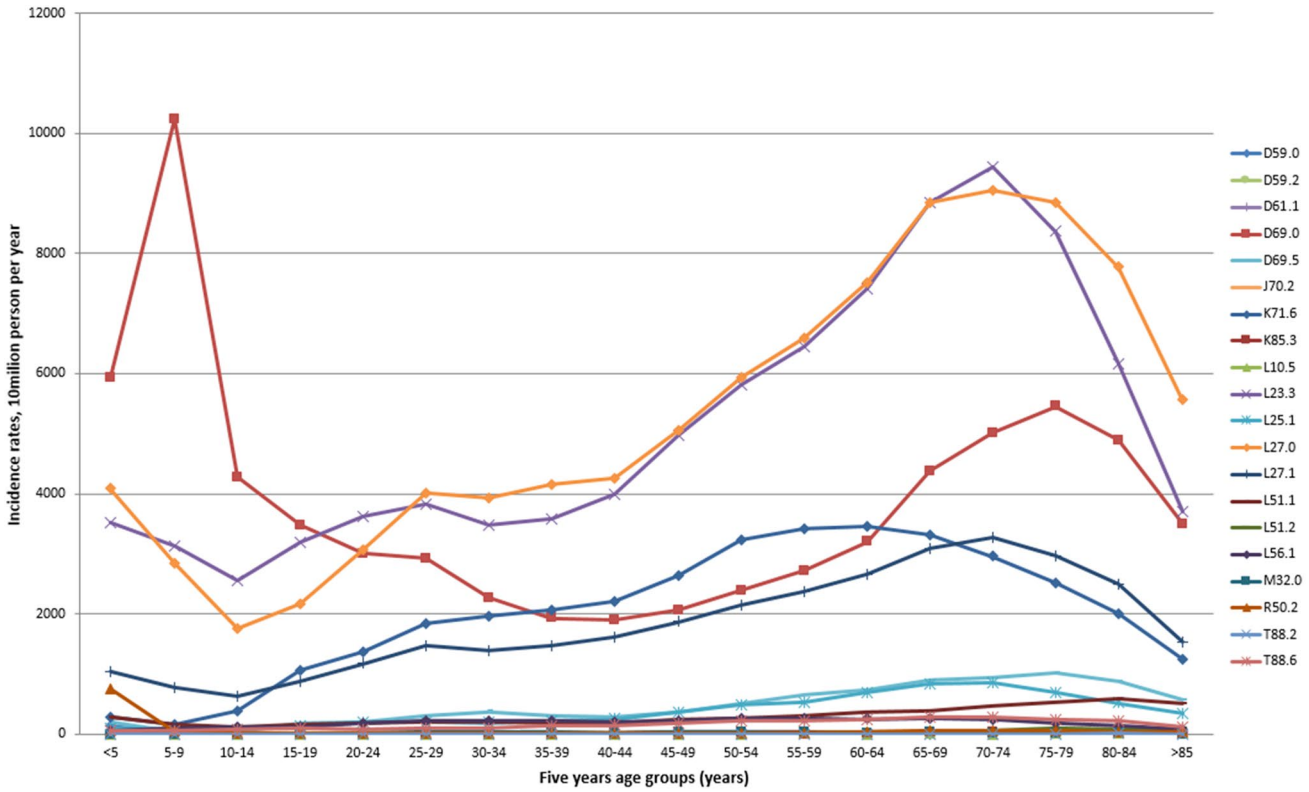

Fig. 2 Six-year incidence rates (crude) for 5-year age groups

3389/10MPY), and toxic liver disease with hepatitis (K71.6, 2046/10MPY). The age-standardized rates (ASR) for above DHRs were 4320 (L23.3), 4295 (L27.0), 3882 (D69.0), and 1709 (K71.6) per 10MPY, respectively. Drug-induced non-autoimmune hemolytic anemia (D59.2, 2/10MPY and ASR 1/10MPY), acute drug-induced interstitial lung disorders (J70.2, 3/10MPY and ASR 3/10MPY), drug-induced pemphigus (L10.5, 4/10MPY and ASR 3/10MPY), and shock due to anesthesia (T88.2, 2/10MPY and ASR 2/10MPY) were the DHRs associated with the lower IRs (Table 3).

The graph plotted for crude IRs of the DHRs by 5-year age groups showed a slightly cosine curve. Most of DHRs occurred at a lower frequency in the early adolescents and reached a peak incidence for the patients in age 70s. However, allergic purpura (D69.0, 10,248/10MPY) had a peak incidence in the 5–9-year group (Fig. 2, Supplement 1).

A Poisson regression analysis of the IR coefficient revealed that 14 DHRs codes were higher in women, and drug-induced acute pancreatitis (K85.3) was higher incidence in men significantly (Table 4). Drug-induced SLE (M32.0) had a particularly high coefficient (8.30; 95% CI, 6.56–10.49) in women. There was no remarkable change by year; however, DIHA (D59.0) and drug-induced aplastic anemia (D61.1) decreased steadily compared to other DHRs. In analysis by the four age groups, the incidence rates increased with age overall but, those for D59.0, D69.0, and R50.2 decreased with age. The IR coefficients by age were 0.51 (95% CI 0.45–0.57) for DIHA (D59.0), 0.88 (0.87–0.89) for allergic purpura (D69.0), and 0.41 (0.38–0.44) for DIF (R50.2), respectively (Table 4). The IR ratios for the three codes were especially higher in the young age ≤ 19 years (Supplement 2).

The highly diagnosed DHR in ED and ICU was for shock due to anesthesia (T88.2) with 75.71% and 11.43%, respectively. However, the DHR resulting in most frequent ED visits during the study period was generalized skin eruption (L27.0), with a total of 139,330 claims. Most ICU visits, on the other hand, were for anaphylactic shock due to adverse effect of correct drug or medicament properly administered (T88.6) with 184 claims. Severe DHRs of SJS (L51.1) and TEN (L51.2) also had more than 100 claims for ICU visits in 2009–2014 (126 and 110 claims, respectively). The most expensive cost per claim was observed for TEN with 942 ± 39.59 USD (Table 5).

Proportions of DHR with ED or ICU visit out of total claims of each DHR were expressed as odds ratio (OR) with reference to toxic liver disease with hepatitis (K71.6). The DHRs with high ED or ICU visit were drug-induced acute pancreatitis [K85.3, OR ED 3.19 (95% CI 2.79–3.65); ICU 23.35 (15.38–35.46)], shock due to anesthesia [T88.2, ED

Table 4 Incidence rate coefficient of DHR diagnostic codes

ICD-10 code	Incidence rate coefficient (95% CI)		
	Sex	Age	Year
D59.0	1.62 (1.34–1.96)*	0.51 (0.45–0.57)*	0.68 (0.64–0.72)*
D59.2	1.01 (0.58–1.79)	3.82 (2.64–5.47)*	1.00 (0.84–1.19)
D61.1	1.80 (1.34–2.43)*	2.59 (2.20–3.06)*	0.76 (0.69–0.84)*
D69.0	1.44 (1.42–1.46)*	0.88 (0.87–0.89)*	1.01 (1.00–1.01)*
D69.5	1.22 (1.18–1.27)*	1.97 (1.93–2.01)*	1.06 (1.05–1.07)*
J70.2	0.87 (0.58–1.31)	2.75 (2.16–3.53)*	1.02 (0.90–1.15)
K71.6	1.17 (1.16–1.19)*	1.65 (1.63–1.65)*	1.00 (1.00–1.01)*
K85.3	0.44 (0.37–0.52)*	1.92 (1.75–2.10)*	1.02 (0.97–1.06)
L10.5	0.91 (0.63–1.32)	2.20 (1.79–2.69)*	0.86 (0.77–0.96)*
L23.3	1.56 (1.54–1.58)*	1.51 (1.49–1.52)*	0.94 (0.93–0.94)*
L25.1	1.26 (1.21–1.31)*	2.05 (2.01–2.10)*	0.89 (0.88–0.90)*
L27.0	1.36 (1.35–1.38)*	1.57 (1.57–1.58)*	0.98 (0.98–0.99)*
L27.1	1.12 (1.10–1.14)*	1.58 (1.58–1.60)*	0.98 (0.98–0.99)*
L51.1	1.29 (1.23–1.35)*	1.49 (1.46–1.54)*	1.05 (1.04–1.06)*
L51.2	1.15 (0.99–1.34)	2.16 (1.99–2.36)*	1.04 (1.00–1.09)*
L56.1	1.75 (1.66–1.85)*	1.31 (1.28–1.35)*	0.99 (0.97–1.00)
M32.0	8.30 (6.56–10.49)*	1.38 (1.27–1.49)*	0.92 (0.89–0.96)
R50.2	1.19 (1.09–1.31)*	0.41 (0.38–0.44)*	1.03 (1.00–1.05)
T88.2	1.15 (0.70–1.88)	1.88 (1.43–2.46)*	0.97 (0.84–1.12)*
T88.6	1.35 (1.27–1.43)*	1.60 (1.55–1.65)*	0.96 (0.94–0.98)*

DHR drug hypersensitivity reaction, *ICD-10* the International Classification of Disease 10th revision

*Statistical significant data; sex was assessed for female versus male; age versus the younger group; year versus 2009

Table 5 Analyses of DHR claims data for cost and ED or ICU visit rates

ICD-10 code	Cost, mean ± SD (per claim, USD)	Rates of ED or ICU visit, n (%)[a]	
		ED	ICU
D59.0	62 ± 6.93	67 (9.90)	0 (0)
D59.2	212 ± 18.56	25 (22.32)	1 (0.89)
D61.1	583 ± 49.50	121 (29.02)	5 (1.20)
D69.0	56 ± 0.87	58,888 (24.42)	39 (0.02)
D69.5	102 ± 3.58	2346 (8.84)	34 (0.13)
J70.2	419 ± 49.20	47 (28.14)	7 (4.19)
K71.6	149 ± 1.05	35,027 (26.64)	174 (0.13)
K85.3	524 ± 18.72	465 (53.70)	26 (3.00)
L10.5	40 ± 4.42	70 (34.48)	0 (0)
L23.3	11 ± 0.09	128,163 (47.84)	1 (0)
L25.1	11 ± 0.44	11,940 (61.85)	0 (0)
L51.1	215 ± 7.42	7805 (41.71)	126 (0.67)
L51.2	942 ± 39.59	728 (35)	110 (5.29)
L27.0	28 ± 0.45	139,330 (52.39)	24 (0.01)
L27.1	15 ± 0.15	48,201 (55.09)	1 (0)
L56.1	17 ± 0.22	3775 (41.92)	0 (0)
M32.0	62 ± 3.30	838 (26.29)	0 (0)
R50.2	197 ± 12.36	872 (39.09)	6 (0.27)
T88.2	498 ± 78.54	53 (75.71)	8 (11.43)
T88.6	154 ± 5.06	3984 (66.91)	184 (3.09)

[a]'%' means the percentage of ED or ICU visits in the each DHR code prescriptions

ICD-10 the International Classification of Disease 10th revision, *SD* standard deviation, *USD* US dollars, *ED* emergency department, *ICU* intensive care unit

8.58 (4.97–14.83); ICU 97.36 (45.94–206.36)], and anaphylactic shock due to adverse effect [T88.6 ED 5.57 (5.27–5.89); ICU 24.06 (19.53–29.65)]. TEN (L51.2) was more diagnosed in ICU than in ED [ED 1.48 (1.35–1.62); ICU 42.13 (33.05–53.71)]. In contrast, claims of generalized or localized skin eruption (L27.0, L27.1) were more dominant in ED visits [L27.0 ED 3.03 (2.99–3.07); ICU 0.07 (0.04–0.10), L27.1 ED 3.38 (3.32–3.44); ICU 0.009 (0.001–0.06), Table 6].

ED or ICU visits by sex for each DHR did not show a specific tendency and was not statistically significant (Table 7). Among the four age groups (≤ 19, 20–44, 45–64, ≥ 65 years), age-related risk of ED or ICU visits in the older age groups (45 years or older) was higher than in the younger age groups (44 years or younger). The 65-year or older group was especially high in ICU visits (Table 8).

Discussion

There are several target organs for DHRs, and multiple symptoms of DHR have been reported in previous ADR studies [18–20]. Cutaneous symptoms are the most reported DHRs in terms of frequency and risk. In this study, DHR codes for cutaneous symptoms like contact dermatitis, skin eruption, SJS, and TEN were included for the drug-induced DHR. Severe cutaneous adverse reactions (SCARs) such as SJS, TEN, drug eruption with eosinophilia and systemic symptom (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been studied by several investigators in Asia [21–23]. Allergic contact dermatitis (ACD) was also among the frequently reported DHRs in Korea, as identified in this study. Antimicrobial agents and topical medications are the known allergens associated with DHRs; however, the incidence or prevalence of ACD due to drugs in the general population is not yet known [24].

Our data showed the higher incidence rate of DHR with increasing age except DHRs related to blood, such as a drug-induced hemolytic anemia, which were higher incidence in children. The pediatric population might have more sensitization to drug with immature metabolism system than adults [1, 25]. Old age was a risk factor for DHRs [26, 27]. Polypharmacy was also an important risk of DHRs, and

Table 6 Odds ratio of DHR claims data about ED or ICU visits

ICD-10 code	Total (n)	ED (n)	OR	95% CI	*p* value	ICU (n)	OR	95% CI	*p* value
D59.0	677	67	0.30	0.23–0.39	*	0	–	–	–
D59.2	112	25	0.79	0.51–1.23	0.301	1	6.80**	0.94–48.96	0.139
D61.1	417	121	1.13	0.91–1.39	0.274	5	9.16**	3.74–22.39	0.0003
D69.0	241,172	58,888	0.89	0.88–0.90	*	39	0.12	0.09–0.17	*
D69.5	26,549	2346	0.27	0.26–0.28	*	34	0.97	0.67–1.40	0.861
J70.2	167	47	1.08	0.77–1.51	0.661	7	33.01**	15.27–71.39	*
K71.6	131,467	35,027	1	Reference	–	174	1	reference	–
K85.3	866	465	3.19	2.79–3.65	*	26	23.35**	15.38–35.46	*
L10.5	203	70	1.45	1.08–1.94	0.012	0	–	–	–
L23.3	267,881	128,163	2.53	2.49–2.56	*	1	0.003	0.0004–0.02	*
L25.1	19,305	11,940	4.46	4.33–4.61	*	0	–	–	–
L27.0	265,958	139,330	3.03	2.99–3.07	*	24	0.07	0.04–0.10	*
L27.1	87,492	48,201	3.38	3.32–3.44	*	1	0.009	0.001–0.06	*
L51.1	18,713	7805	1.97	1.91–2.03	*	126	5.11	4.07–6.44	*
L51.2	2080	728	1.48	1.35–1.62	*	110	42.13**	33.05–53.71	*
L56.1	9006	3775	1.99	1.90–2.08	*	0	–	–	–
M32.0	3187	838	0.98	0.91–1.06	0.660	0	–	–	–
R50.2	2231	872	1.77	1.62–1.93	*	6	2.03**	0.90–4.60	0.131
T88.2	70	53	8.58	4.97–14.83	*	8	97.36**	45.94–206.36	*
T88.6	5954	3984	5.57	5.27–5.89	*	184	24.06	19.53–29.65	*

ICD-10 the International Classification of Disease 10th revision, *ED* emergency department, *ICU* intensive care unit, *OR* odds ratio, *CI* confidence interval

*< 0.0001; **Fisher's exact test was performed

DHR-related drug therapy was more reported in the elderly [20, 28–30].

DIHA, allergic purpura, and drug-induced fever (DIF) were more frequently diagnosed in the young age groups. There is a few reported data for DIHA as a rare incidence in the general population. A study on children reported that over 65% of autoimmune hemolysis occurred in children < 5 years with ceftriaxone as the most frequent culprit drug [31, 32]. In our study, DIF was also frequent in the < 5-year group (58.84%), with the higher IRs in young age group, while drug fever may have been underestimated in the adult age group as a general manifestation appearing along with other symptoms. Vaccination may also contribute to this observation as children are vaccinated against numerous pathogens until approximately 5 years after birth, and they occasionally experience fever as a typical ADR to vaccines [33–35]. Allergic purpura was also high in the 5–9-year age group. Previous surveillance studies on immunoglobulin A vasculitis (Henoch–Schönlein purpura), a representative manifestation of allergic purpura, reported high incidence in the 5–10 years [36].

Women experienced DHRs higher than men for most of DHRs as reported in other previous studies. Drug-induced SLE had the highest IR coefficient, 8.30 (95% CI 6.56–10.49) in the female in this study. A epidemiologic study in a predominantly white population in the USA reported an SLE incidence rate of 5.1 per 100,000 (95% CI 3.5–6.6) in the female and 0.8 per 100,000 (0–1.6) in the male [37].

Shock to anesthesia was the highest cause for both ED and ICU visits. According to the published epidemiologic data, mortality associated with anaphylaxis during surgeries was in the range of 0–9% [38–41]. The physical condition due to surgery and anesthesia-induced cardiopulmonary dysfunction are known risk factors for anaphylaxis during surgery [42]. This study showed a different trend in visits to ED or ICU by DHRs. A comparative study about characteristics of the elderly visiting a medical ED in Korea showed that 55.5% of patients visited ED directly for urgent and immediate medical care without transfer through other medical institutions and 46.6% visits by walking [43]. Skin eruption was a symptom easily perceived by the patient and was ranked as 4th and 6th of ED visit with rare ICU visit in this study. ICU care is needed for critically ill patients who need hourly and/or invasive monitoring [44]. TEN is one of the severe DHRs, which was more prominent ICU than ED in this study. The mortality rate at 6 weeks of TEN was reported 46% in RegiSCAR (International Registry of Severe Cutaneous Adverse Reaction) group study [45]. The rate of ICU or ED visits was also high in the elderly. A prospective cohort study in Taiwan reported that the proportion of ADRs leading to ED visits in the older age group was

Table 7 Gender-related risk of DHR claims data with ED or ICU visits

ICD-10 code	Gender	Total (n, %)	ED (n, %)	RR	95% CI	*p* value	ICU (n, %)	RR	95% CI	*p* value
D59.0	Male	252 (37.2)	21 (31.3)	1	–	–	0 (0)	–	–	–
	Female	425 (62.8)	46 (68.7)	1.30	0.79–2.12	0.29	0 (0)	–	–	–
D59.2	Male	53 (47.3)	7 (28.0)	1	–	–	0 (0)	–	–	–
	Female	59 (52.7)	18 (72.0)	2.31	1.05–5.09	0.028	1 (100)	–	–	–
D61.1	Male	151 (36.2)	52 (43.0)	1	–	–	3 (60.0)	1	–	–
	Female	266 (63.8)	69 (57.0)	0.75	0.56–1.02	0.066	2 (40.0)	0.38**	0.06–2.24	0.357
D69.0	Male	105,156 (43.6)	26,699 (45.3)	1	–	–	31 (79.5)	1	–	–
	Female	136,016 (56.4)	32,189 (54.7)	0.93	0.92–0.95	*	8 (20.5)	0.20	0.09–0.43	*
D69.5	Male	11,800 (44.4)	985 (42.0)	1	–	–	14 (41.2)	1	–	–
	Female	14,749 (55.6)	1361 (58.0)	1.11	1.02–1.20	0.012	20 (58.8)	1.14	0.58–2.26	0.701
J70.2	Male	92 (55.1)	24 (51.1)	1	–	–	6 (85.7)	1	–	–
	Female	75 (44.9)	23 (48.9)	1.18	0.72–1.91	0.512	1 (14.3)	0.20**	0.03–1.66	0.131
K71.6	Male	59,929 (45.6)	15,387 (43.9)	1	–	–	90 (51.7)	1	–	–
	Female	71,538 (54.4)	19,640 (56.1)	1.07	1.05–1.09	*	84 (48.3)	0.78	0.58–1.05	0.104
K85.3	Male	611 (70.6)	349 (75.1)	1	–	–	21 (80.8)	1	–	–
	Female	255 (29.4)	116 (24.9)	0.80	0.68–0.93	0.002	5 (19.2)	0.57	0.22–1.50	0.246
L10.5	Male	107 (52.7)	40 (57.1)	1	–	–	0 (0)	–	–	–
	Female	96 (47.3)	30 (42.9)	0.84	0.57–1.23	0.359	0 (0)	–	–	–
L23.3	Male	112,572 (42.0)	55,545 (43.3)	1	–	–	1 (100)	–	–	–
	Female	155,309 (58.0)	72,618 (56.7)	0.95	0.94–0.96	*	0 (0)	–	–	–
L25.1	Male	9029 (46.8)	5546 (46.4)	1	–	–	0 (0)	–	–	–
	Female	10,276 (53.2)	6394 (53.6)	1.01	0.99–1.04	0.255	0 (0)	–	–	–
L27.0	Male	117,278 (44.1)	59,213 (42.5)	1	–	–	12 (50.0)	1	–	–
	Female	148,680 (55.9)	80,117 (57.5)	1.07	1.06–1.08	*	12 (50.0)	0.79	0.35–1.76	0.560
L27.1	Male	44,507 (50.9)	25,865 (53.7)	1	–	–	1 (100)	–	–	–
	Female	42,985 (49.1)	22,336 (46.3)	0.89	0.88–0.91	*	0 (0)	–	–	–
L51.1	Male	7991 (42.7)	3222 (41.3)	1	–	–	61 (48.4)	1	–	–
	Female	10,722 (57.3)	4583 (58.7)	1.06	1.02–1.10	*	65 (51.6)	0.79	0.56–1.12	0.194
L51.2	Male	927 (44.6)	329 (45.2)	1	–	–	55 (50.0)	1	–	–
	Female	1153 (55.4)	399 (54.8)	0.98	0.87–1.10	0.674	55 (50.0)	0.80	0.56–1.16	0.239
L56.1	Male	3658 (40.6)	1674 (44.3)	1	–	–	0 (0)	–	–	–
	Female	5348 (59.4)	2101 (55.7)	0.86	0.82–0.90	*	0 (0)	–	–	–
M32.0	Male	225 (7.1)	44 (5.3)	1	–	–	0 (0)	–	–	–
	Female	2962 (92.9)	794 (94.7)	1.37	1.04–1.80	0.017	0 (0)	–	–	–
R50.2	Male	1017 (45.6)	434 (49.8)	1	–	–	1 (16.7)	1	–	–
	Female	1214 (54.4)	438 (50.2)	0.85	0.76–0.94	0.002	5 (83.3)	4.19**	0.49–35.79	0.229
T88.2	Male	34 (48.6)	25 (47.2)	1	–	–	2 (25.0)	1	–	–
	Female	36 (51.4)	28 (52.8)	1.06	0.81–1.38	0.679	6 (75.0)	2.83**	0.61–13.09	0.261
T88.6	Male	2517 (42.3)	1696 (42.6)	1	–	–	78 (42.4)	1	–	–
	Female	3437 (57.7)	2288 (57.4)	0.99	0.95–1.02	0.511	106 (57.6)	0.10	0.75–1.33	0.974

ICD-10 the International Classification of Disease 10th revision, *ED* emergency department, *ICU* intensive care unit, *RR* relative risk, *CI* confidence interval

*< 0.0001; **Fisher's exact test was performed

14.3 per 1000 and the younger group was 4.1 per 1000 [46]. Because geriatric populations have multiple diseases and weaken physical condition, immediate treatment is required when symptoms occur.

This study has strength as an epidemiologic research for DHRs of the general population in Korea. DHRs are relatively uncommon, and studies are usually limited in sample size. This study on incidence of DHRs on nearly entire Korean population for 6 years increases the strength

Table 8 Age-related risk of DHR claims data with ED or ICU visits

ICD-10 code	Age	Total (n, %)	ED (n, %)	RR	95% CI	*p* value	ICU (n, %)	RR	95% CI	*p* value
D59.0	≤19	370 (54.7)	22 (32.8)	0.41	0.25–0.66	0.0002	0 (0)	–	–	–
	20–44	80 (11.8)	10 (14.9)	1.31	0.70–2.46	0.406	0 (0)	–	–	–
	45–64	87 (12.9)	8 (11.9)	0.92	0.46–1.86	0.815	0 (0)	–	–	–
	≥65	140 (20.7)	27 (40.3)	2.59	1.65–4.07	*	0 (0)	–	–	–
D59.2	≤19	1 (0.9)	0 (0)	–	–	–	0 (0)	–	–	–
	20–44	15 (13.4)	0 (0)	–	–	–	0 (0)	–	–	–
	45–64	47 (42)	11 (44.0)	1.09	0.54–2.18	0.815	0 (0)	–	–	–
	≥65	49 (43.8)	14 (56.0)	1.64	0.82–3.28	0.161	1 (100)	–	–	–
D61.1	≤19	6 (1.4)	3 (2.5)	1.17**	0.77–3.93	0.362	0 (0)	–	–	–
	20–44	106 (25.4)	12 (9.9)	0.32	0.19–0.56	*	0 (0)	–	–	–
	45–64	194 (46.5)	65 (53.7)	1.33	0.99–1.80	0.060	2 (40.0)	0.77**	0.13–4.54	1
	≥65	111 (26.6)	41 (33.9)	1.41	1.04–1.92	0.032	3 (60.0)	4.14**	0.70–24.42	0.120
D69.0	≤19	102,077 (42.3)	17,213 (29.2)	0.56	0.55–0.57	*	17 (45.6)	1.05	0.56–1.98	0.873
	20–44	58,015 (24.1)	14,001 (23.8)	0.98	0.97–1.00	0.068	2 (5.1)	0.17	0.04–0.71	0.006
	45–64	4,5874 (19)	15,410 (26.2)	1.51	1.49–1.53	*	6 (15.4)	0.77	0.32–1.85	0.563
	≥65	35,206 (14.6)	12,264 (20.8)	1.54	1.51–1.56	*	14 (35.9)	3.28	1.70–6.30	0.0002
D69.5	≤19	1638 (6.2)	177 (7.5)	1.24	1.07–1.43	0.004	3 (8.8)	1.47**	0.45–4.81	0.465
	20–44	7520 (28.3)	425 (18.1)	0.56	0.51–0.62	*	1 (2.9)	0.08	0.01–0.56	0.001
	45–64	10,310 (38.8)	889 (37.9)	0.96	0.89–1.04	0.328	8 (23.5)	0.48	0.22–1.07	0.067
	≥65	7081 (26.7)	855 (36.5)	1.58	1.46–1.71	*	22 (64.7)	5.04	2.50–10.18	*
J70.2	≤19	21 (12.6)	3 (6.4)	0.47	0.16–1.39	0.131	0 (0)	–	–	–
	20–44	18 (10.8)	9 (19.2)	1.96	1.15–3.36	0.030	0 (0)	–	–	–
	45–64	43 (25.8)	9 (19.2)	0.68	0.36–1.29	0.222	1 (14.3)	0.48**	0.06–3.88	0.679
	≥65	85 (50.9)	26 (55.3)	1.19	0.73–1.95	0.475	6 (85.7)	5.79**	0.71–47.04	0.118
K71.6	≤19	5741 (4.4)	1506 (4.3)	0.98	0.94–1.03	0.472	4 (2.3)	0.52	0.19–1.39	0.182
	20–44	43,170 (32.8)	12,321 (35.2)	1.11	1.10–1.13	*	39 (22.4)	0.59	0.41–0.84	0.003
	45–64	60,595 (46.1)	15,370 (43.9)	0.91	0.90–0.93	*	75 (43.1)	0.89	0.66–1.20	0.429
	≥65	21,961 (16.7)	5830 (16.6)	1.00	0.97–1.02	0.724	56 (32.2)	2.37	1.72–3.25	*
K85.3	≤19	35 (4.0)	8 (1.7)	0.42	0.23–0.77	0.0002	0 (0)	–	–	–
	20–44	252 (29.1)	158 (34.0)	1.25	1.11–1.42	0.0007	6 (23.1)	0.73	0.30–1.80	0.492
	45–64	410 (47.3)	219 (47.1)	0.99	0.87–1.12	0.875	15 (57.7)	1.52	0.70–3.26	0.283
	≥65	169 (19.5)	80 (17.2)	0.86	0.72–1.02	0.065	5 (19.2)	0.98	0.38–2.57	0.970
L10.5	≤19	13 (6.4)	5 (7.1)	1.12**	0.55–2.99	0.769	0 (0)	–	–	–
	20–44	42 (20.7)	18 (25.7)	1.33	0.88–2.01	0.200	0 (0)	–	–	–
	45–64	89 (43.8)	23 (32.9)	0.63	0.41–0.95	0.022	0 (0)	–	–	–
	≥65	59 (29.1)	24 (34.3)	1.27	0.86–1.88	0.235	0 (0)	–	–	–
L23.3	≤19	31,324 (11.7)	4166 (3.3)	0.25	0.25–0.26	*	0 (0)	–	–	–
	20–44	71,825 (26.8)	25,322 (19.8)	0.67	0.66–0.68	*	0 (0)	–	–	–
	45–64	98,973 (37)	57,633 (45.0)	1.39	1.38–1.41	*	1 (100)	–	–	–
	≥65	65,759 (24.6)	41,042 (32.0)	1.45	1.44–1.46	*	0 (0)	–	–	–
L25.1	≤19	950 (4.9)	258 (2.2)	0.43	0.38–0.47	*	0 (0)	–	–	–
	20–44	4186 (21.7)	2264 (19.0)	0.85	0.82–0.87	*	0 (0)	–	–	–
	45–64	8362 (43.3)	5570 (46.7)	1.14	1.12–1.17	*	0 (0)	–	–	–
	≥65	5807 (30.1)	3848 (32.2)	1.11	1.08–1.13	*	0 (0)	–	–	–
L27.0	≤19	25,294 (9.5)	6685 (4.8)	0.48	0.47–0.49	*	1 (4.2)	0.41**	0.06–3.06	0.723
	20–44	78,014 (29.3)	41,549 (29.8)	1.02	1.02–1.03	*	3 (12.5)	0.34	0.10–1.15	0.070
	45–64	98,095 (36.9)	57,067 (41.0)	1.19	1.18–1.20	*	9 (37.5)	1.03	0.45–2.35	0.950
	≥65	64,555 (24.3)	34,029 (24.4)	1.01	1.00–1.02	0.057	11 (45.8)	2.64	1.18–5.89	0.014
L27.1	≤19	7492 (8.6)	1951 (4.1)	0.45	0.43–0.47	*	0 (0)	–	–	–
	20–44	26,902 (30.8)	13,794 (28.6)	0.90	0.89–0.92	*	1 (100)	–	–	–

Table 8 (continued)

ICD-10 code	Age	Total (n, %)	ED (n, %)	RR	95% CI	*p* value	ICU (n, %)	RR	95% CI	*p* value
	45–64	32,878 (37.6)	20,337 (42.2)	1.21	1.20–1.23	*	0 (0)	–	–	–
	≥65	20,220 (23.1)	12,119 (25.1)	1.12	1.10–1.13	*	0 (0)	–	–	–
L51.1	≤19	2365 (12.6)	702 (9.0)	0.68	0.64–0.73	*	9 (7.1)	0.53	0.27–1.05	0.063
	20–44	5845 (31.2)	2196 (28.1)	0.86	0.83–0.90	*	17 (13.5)	0.34	0.21–0.57	*
	45–64	6317 (33.8)	2997 (38.4)	1.22	1.18–1.27	*	37 (29.4)	0.82	0.56–1.20	0.296
	≥65	4186 (22.4)	1910 (24.5)	1.12	1.08–1.17	*	63 (50.0)	3.47	2.45–4.91	*
L51.2	≤19	208 (10.0)	70 (9.6)	0.96	0.78–1.17	0.668	15 (13.6)	1.42	0.84–2.40	0.19
	20–44	576 (27.7)	157 (21.6)	0.72	0.62–0.83	*	11 (10.0)	0.29	0.16–0.54	*
	45–64	766 (36.8)	260 (35.7)	0.95	0.84–1.08	0.440	25 (22.7)	0.50	0.33–0.78	0.002
	≥65	530 (25.5)	241 (33.1)	1.45	1.29–1.63	*	59 (53.6)	3.38	2.36–4.86	*
L56.1	≤19	842 (9.4)	140 (3.7)	0.37	0.32–0.44	*	0 (0)	–	–	–
	20–44	3374 (37.5)	1161 (30.8)	0.74	0.70–0.78	*	0 (0)	–	–	–
	45–64	3375 (37.5)	1670 (44.2)	1.32	1.26–1.39	*	0 (0)	–	–	–
	≥65	1415 (15.7)	804 (21.3)	1.45	1.38–1.53	*	0 (0)	–	–	–
M32.0	≤19	138 (4.3)	11 (1.3)	0.29	0.17–0.52	*	0 (0)	–	–	–
	20–44	1355 (42.5)	166 (19.8)	0.33	0.29–0.39	*	0 (0)	–	–	–
	45–64	1357 (42.6)	565 (67.4)	2.79	2.46–3.17	*	0 (0)	–	–	–
	≥65	337 (10.6)	96 (11.5)	1.09	0.91–1.31	0.334	0 (0)	–	–	–
R50.2	≤19	1359 (60.9)	451 (51.7)	0.69	0.62–0.76	*	0 (0)	–	–	–
	20–44	340 (15.2)	137 (15.7)	1.04	0.90–1.19	0.620	1 (16.7)	1.11**	0.13–9.49	1.000
	45–64	297 (13.3)	164 (18.8)	1.51	1.34–1.70	*	3 (50.0)	6.51**	1.32–32.11	0.034
	≥65	235 (10.5)	120 (13.8)	1.36	1.18–1.56	*	2 (33.3)	4.25**	0.78–23.06	0.125
T88.2	≤19	5 (7.1)	5 (9.4)	1.35**	1.17–1.57	0.326	0 (0)	–	–	–
	20–44	22 (31.4)	18 (34.0)	1.12	0.86–1.46	0.420	5 (62.5)	3.64**	0.95–13.88	0.098
	45–64	26 (37.1)	17 (32.1)	0.80	0.58–1.09	0.121	2 (25.0)	0.56**	0.12–2.59	0.701
	≥65	17 (24.3)	13 (24.5)	1.01**	0.75–1.37	1	1 (12.5)	0.45**	0.06–3.37	0.669
T88.6	≤19	792 (13.3)	385 (9.7)	0.70	0.65–0.75	*	6 (3.3)	0.22	0.10–0.49	*
	20–44	1831 (30.8)	1218 (30.6)	0.99	0.95–1.03	0.668	44 (23.9)	0.71	0.51–0.99	0.041
	45–64	2255 (37.9)	1592 (40.0)	1.09	1.05–1.13	*	67 (36.4)	0.94	0.70–1.26	0.678
	≥65	1076 (18.1)	789 (19.8)	1.12	1.07–1.17	*	67 (36.4)	2.60	1.94–3.48	*

Fisher's exact test or Chi-square test for 2 × 2 contingency table in which each age group was compared with other age groups combined

ICD-10 the International Classification of Disease 10th revision, *ED* emergency department, *ICU* intensive care unit, *RR* relative risk, *CI* confidence interval

*< 0.0001; **Fisher's exact test was performed

of the study. In addition, analysis of incidence according to age, sex, and year of DHR occurrence further increases our understanding of the DHR characteristics in the Korean population. Analyzing ICU or ED visit for each DHR also added information regarding to medical resource utilization from this study.

We also have carried out a separate study not published yet to analyze data of the Korean pharmacovigilance centers to where the spontaneous reports of DHR were reported. Out of total 662,160 ADR reports during 1989–2014, 17.7% (116,209) were the DHRs with WHO-adverse reaction terminology codes. The data of spontaneous reports could not be compared directly to the results of this study with HIRA claim data assessing incidence of DHRs in the Koreans (around 0.18%, 90,000 patients out of 50,000,000 population).

There are some limitations in this study based on the insurance claim data. We were unable to verify information such as clinical laboratory data, family and social history, and other supporting clinical data. Although the ICD-10 codes have been used for a long time since 1990, classification of some allergic diseases is often difficult to use the ICD-10 codes because of uncertain terminologies. For this reason, DHRs without ICD-10 codes were not included in this study, although DHR associated symptoms were present. Furthermore, there is a possibility of under-coding or over-coding for a certain diagnosis. The lack of analysis of the causative drug is also the limit of this study. The claim

data with DHRs included the medications, such as steroids or antihistamines, to treat the DHR when the prescriptions were analyzed. The further analysis is in progress performed for the suspected drug using the claim data which included the prescriptions for 6 months prior to the index date of DHR event in each patient during the study period. If research is conducted on the causative drug, it will be more helpful to understand the current state of DHR in Korea. According to a WHO report, ICD-11 will be released in 2018. The allergist communities are reviewing the adequacy of the new codes and have proposed their professional opinion [47–49]. The category of drug hypersensitivity was added, the new diagnostic codes were formed, and the existing diagnostic codes were subdivided [50]. These efforts in the newly constructed diagnostic codes may improve the quality of epidemiologic research. This study warrants the health professionals should have more efforts to identify or prevent DHRs with review of any known drug allergy using information technology in the computerized prescription order entry of the electronic medical record system. In the future, a genetic testing prior to use of the high-risk drug like abacavir can prevent the severe life-threatening DHRs.

Conclusion

The major diagnostic codes of drug hypersensitivity reactions were allergic contact dermatitis, generalized skin eruption, allergic purpura, and toxic liver disease with hepatitis in Korea. Female showed a higher DHR than male, and the incidence generally increased with age. However, drug-induced autoimmune hemolytic anemia, allergic purpura, and drug-induced fever occurred at a higher frequency in the younger age group. Severe cutaneous adverse reactions, anaphylaxis, or shock was diagnosed highly in ED and ICU. DHRs leading to ICU and ED visits were also high in the elderly. Future efforts to prevent DHRs including severe events should be implemented in the health care system through application of information technology and the advanced knowledge of pharmacogenomics associated DHRs.

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