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Review of Ototoxic Drugs Using Health Insurance Data: A Data-Driven Management System

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Abstract

Objective. With more than 1.57 billion people affected by hearing loss worldwide, this study investigates the association between ototoxic drug use and hearing loss, utilizing South Korean national health data. The goal is to inform clinical prevention and management guidelines by identifying ototoxic drugs and assessing their risks.

Study Design. This study is a retrospective observational study using the Health Insurance Review and Assessment Service (HIRA) to analyze the association between suspected ototoxic drug use and hearing loss.

Setting. Data were obtained from the National Patient Samples (NPS) of HIRA in South Korea, covering 2009 to 2016. The study included all National Health Insurance (NHI) enrollees with at least one hospital visit.

Methods. Patients diagnosed with suspected ototoxicity hearing loss (SOHL) were identified, and ototoxic drugs were reviewed using national data. Of 491 reviewed ingredients, 151 were suspected ototoxic. Logistic regression and Cox proportional hazards models assessed associations between drug prescriptions and SOHL, analyzed with SAS 9.4.

Results. SOHL patients were older, with higher rates of underlying conditions and medication use compared to controls. The odds ratio (OR) for SOHL was significantly elevated in patients aged ≥65, increasing from 3.007 to 3.366. Proton pump inhibitors (PPIs) and antibiotics presented elevated risks, especially in older adults, with hazard ratios (HRs) for PPIs rising from 1.85 to 2.90. Notably, PPIs posed higher risks for patients <65.

Conclusion. The study confirms that factors like age, gender, underlying diseases, and specific medications increase SOHL risk, emphasizing the need for cautious medication use tailored to age.

Keywords

medication usage, ototoxicity hearing loss, risk factors, suspected ototoxicity hearing loss (SOHL)

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Hearing loss (HL) is one of the most common sensory impairments worldwide, with approximately 1.57 billion people suffering from HL as of 2019. Owing to factors such as aging and noise exposure, an estimated 2.45 billion people are projected to experience HL by 2050.[1]

The causes of HL are not entirely clear; however, some cases are attributed to noise, ototoxic drugs, and aging. Ototoxicity hearing loss (OHL) occurs when ototoxic drugs generate reactive oxygen species (ROS) and damage mitochondria at the cellular level, leading to toxicity in the inner ear, particularly in the cochlea and vestibular system, impairing auditory function. Key ototoxic drugs include aminoglycoside antibiotics, loop diuretics, and cisplatin-based chemotherapy agents.[2,3]

In recent years, the incidence of OHL has increased with the rise in new drugs and combination therapies.[2,4,5] The development of ototoxic drugs is inevitable, and national or academic warnings and guidelines regarding these drugs are essential. However, the composition of drugs varies by country, and while some countries conduct systematic research and national management of ototoxic drugs.[6,7] South Korea currently lacks a compiled list of such drugs, making it challenging to systematically monitor and manage their use.

Although hearing tests should be performed immediately after drug administration, diagnosing OHL is difficult in the early stages. This study defined suspected ototoxicity hearing loss (SOHL) using an operational definition and analyzed the patient group to explore the relationship between drug use and HL. Moreover, as

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ototoxic side effects can occur with various compounds beyond specific drug classes, broad exploration of all drug ingredients is necessary.

This study aimed to analyze the status of ototoxic drug use in South Korea using data from the Health Insurance Review and Assessment Service (HIRA). The HIRA database includes comprehensive health care information collected across South Korea and provides active ingredient data, allowing for the analysis of all drugs used in the country.[8] By utilizing these, this study examined the current usage of ototoxic drugs and assessed the risk of OHL and investigated not only well-known ototoxic drugs but also the use and potential ototoxic side effects of newer drugs, such as proton pump inhibitors (PPIs), which have recently gained attention as suspected ototoxic drugs.[9-11] Further, this study aimed to establish a list of ototoxic drugs in South Korea and contribute to the development of effective strategies for the prevention and management of OHL.

Materials and Methods

Data Collection and Participants

This study analyzed the National Patient Samples (NPS) provided by HIRA, based on hospital visit records of patients enrolled in the National Health Insurance (NHI) from 2009 to 2016.[8] The sample included all NHI enrollees who visited the hospital at least once during the study period. Patients diagnosed with ototoxicity-related HL or prescribed specific drugs associated with ototoxicity were selected for the study. The study was approved by the Institutional Review Board (CR323353) of Yonsei University Wonju Severance Christian Hospital (Wonju, Republic of Korea).

Study Design

This study established a research database based on the HIRA-NPS, using two criteria. First, patients who had been prescribed suspected ototoxic drugs, classified by their therapeutic effects, at least once, were included. Second, patients diagnosed with OHL based on the primary diagnosis codes H91.0, H90.3, H90.4, H90.5, H91.2, H91.3, H91.8, and H91.9 from the International Classification of Diseases 10th (ICD-10) were included.

Using this database, the general characteristics of the SOHL patient and control groups were compared, and a retrospective analysis was conducted to evaluate the association between SOHL diagnosis and drug prescriptions using logistic regression and survival analyses (**Figure 1**).

To establish the criteria for drug use, drugs were classified based on the main active ingredients of suspected ototoxic drugs. A review of the single-component drugs prescribed before OHL diagnosis revealed a total of 491 active ingredients, of which 151 suspected ototoxic ingredients were selected as the criteria for drug use.

As a result, a research database built using HIRA-NPS data was used to analyze the risk of SOHL occurrence based on demographic characteristics and drug prescription history.

Operational Definition

OHL and Medical History

In this study, the clarity of the OHL diagnosis was questioned; therefore, the SOHL patient group was defined separately. The SOHL patient group consisted of patients who had recorded at least once in their medical records as the primary diagnosis variable for OHL

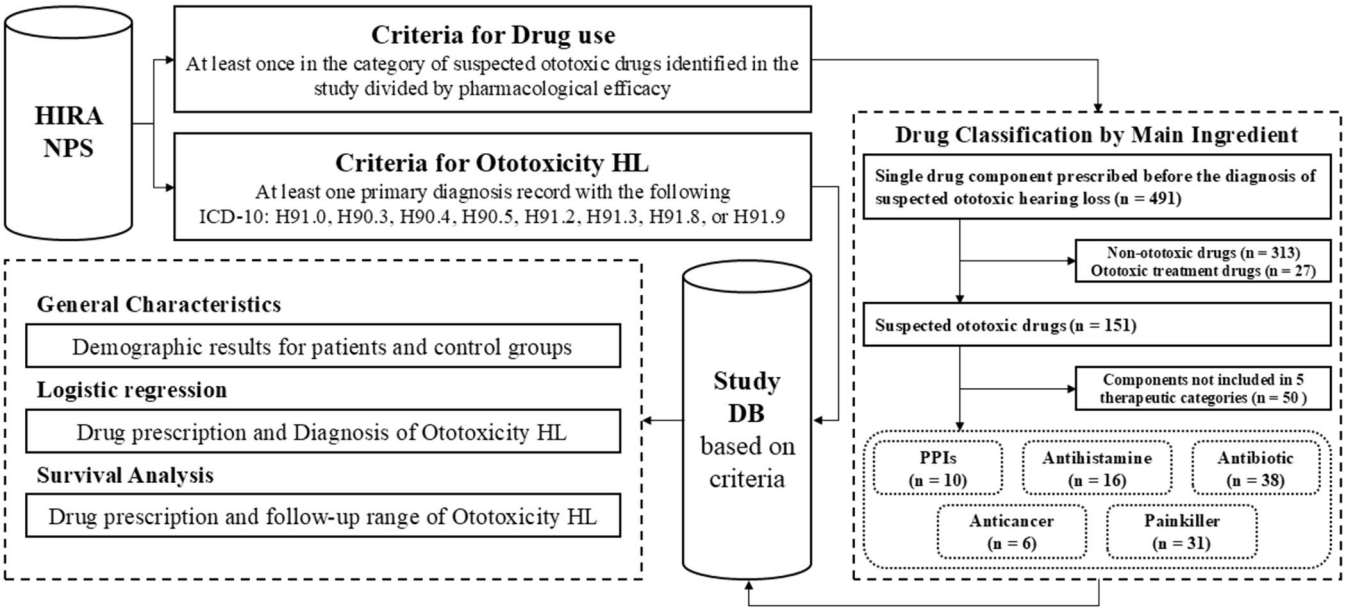

Figure 1. Study flow chart. DB, Database; HIRA, Health Insurance Review and Assessment Service; HL, hearing loss; ICD-10, International Classification of Diseases 10th; NPS, National Patient Samples; PPIs, proton pump inhibitors.

(H91.0), codes for sensorineural and sudden HL (H90.3, H90.4, H90.5, and H91.2), or cases classified under other HL codes (H91.3, H91.8, and H91.9) for unspecified HL or deafness not otherwise classified (Supplement 1, available online).

For the analysis of medical history, hypertension, diabetes mellitus, other vascular diseases, and chronic kidney disease were considered. A patient was deemed to have a medical history if they had been diagnosed with the corresponding disease codes as a primary diagnosis at least once.[12] For the SOHL patient group, the medical history before the date of HL diagnosis was confirmed for each patient, whereas for the control group, the medical history could not be verified and was substituted with medical history records.

Ototoxic Drug Ingredients

Based on the medical records of patients with OHL, potential key components that may induce OHL were extracted. Using the date of the first HL diagnosis as a reference, all active ingredient codes of medications prescribed in previous medical records from 2009 to 2016 were compiled without duplication. Additionally, the ingredient names of medications distributed in South Korea corresponding to the active ingredient codes were investigated through various sources, including Druginfo,[13] the World Health Organization Collaborating Centers (WHOCC), and Korea Pharmaceutical Information Service (KPIS).

As a result, a total of 491 single ingredient names prescribed before the diagnosis of SOHL were identified (**Figure 1**). These ingredient names were categorized based on previous research, namely suspected ototoxicity drugs,[14-17] ototoxic treatment drugs,[18-20] and nonototoxic ingredients, with each category comprising 151, 313, and 27 ingredient names, respectively, whereas ingredients that did not cause OHL and those used for OHL treatment were excluded from this study.

The 151 suspected ototoxic ingredients were classified based on their therapeutic effects, referred to as "TYPE" in this study. The main types selected were antibiotics, anticancer agents, antihistamines, painkillers, and PPIs. The ingredient names within each TYPE were chosen based on reported ototoxicity risk information from existing studies.[9-11,21-24] This resulted in the classification of 10 PPIs, 16 antibiotics, 38 antihistamines, 6 anticancer agents, and 31 painkillers (Supplement 2, available online).

For mixed medications containing single ingredients from the five selected TYPES, the active ingredient codes were included in each TYPE based on the ingredients' classification. If a patient had taken at least one ingredient from any TYPE during the year, they were considered to have used medication from that TYPE.

Statistical Methods

The statistical analysis methods used in this study included logistic regression and frequency analyses for categorical variables. To compare the general characteristics of the SOHL patient and control groups, frequency analysis was conducted using the chi-square test. Hazard ratios (HRs) were calculated using Cox's proportional hazard model, with duration defined as the difference between the start and end dates of drug prescriptions.[25] All statistical analyses were performed using SAS version 9.4.

In the frequency analysis comparing general characteristics, the patient group consisted of individuals diagnosed with at least one of the four types of HL, including OHL, as the primary diagnosis. The control group consisted of patients without ear, nose, and throat (ENT) consultation records. In the South Korean health care system, patients can directly access ENT specialists even in primary care settings without requiring a referral. As a result, individuals experiencing auditory symptoms such as HL typically visit ENT clinics for evaluation. Given this health care structure, the absence of ENT consultation records strongly suggests that the individuals did not experience clinically significant hearing issues. Additionally, the same patient and control groups were used to calculate odds ratios (ORs) when analyzing the relationship between drug prescription history and SOHL occurrence. Cox regression was performed on patients who had been prescribed the five types of ingredients defined above at least once to assess the HR for SOHL. Patients with a drug prescription duration of zero were excluded from this analysis, allowing for the examination of the relationship between drug use and the occurrence of HL.

Results

The general characteristics of the SOHL patient and control groups without ENT records are compared in **Table 1**. The proportion of males in the SOHL group decreased from 47.6% in 2009 to 46.3% in 2016, whereas the proportion of those aged 65 years and older increased from 34.1% in 2009 to 41.4% in 2016. In contrast, the proportion of men in the control group was higher; the proportion of patients aged 65 years and older was lower.

Regarding medical history, the SOHL group had higher proportions than the control group across all items, with the most notable difference observed in hypertension, where both groups had high rates. Medication usage was significantly higher in the SOHL group (more than 96%) than in the control group (more than 92%). Both groups experienced a temporary decrease in medication use in 2013, but this was followed by recovery.

The results of the chi-square test indicated significant differences between the groups for all values except for gender in 2009 ($P < .0001$), suggesting that the SOHL group had a higher proportion of older adults and underlying diseases, and a higher rate of medication usage than the control group.

Table 1. General Characteristics Between Suspected Ototoxicity Hearing Loss Group and Control Group

		2009	2010	2011	2012	2013	2014	2015	2016
SOHL group	Sex (male) (%)	4943[a] (47.6)	5122 (45.6)	5087 (46.1)	5166 (45.8)	5365 (46.3)	5511 (45.9)	5980 (46.0)	6859 (46.3)
	Age group (%)	3547 (34.1)	3859 (34.3)	3662 (33.2)	3817 (33.9)	4077 (35.2)	4244 (35.3)	4848 (37.3)	6130 (41.4)
	Diseases (%)								
	HTN	2571 (24.7)	2811 (25.0)	2730 (24.7)	2715 (24.1)	2881 (24.8)	2756 (23.0)	3169 (24.4)	3803 (25.7)
	DM	1105 (10.6)	1196 (10.6)	1241 (11.3)	1272 (11.3)	1231 (10.6)	1322 (11.0)	1486 (11.4)	1819 (12.3)
	OVD	402 (3.9)	416 (3.7)	404 (3.7)	445 (4.0)	402 (3.5)	520 (4.3)	571 (4.4)	724 (4.9)
	CKD	65 (0.6)	82 (0.7)	91 (0.8)	114 (1.0)	102 (0.9)	112 (0.9)	139 (1.1)	227 (1.5)
	Drug (%)	9982 (96.0)	10,807 (96.1)	10,630 (96.3)	10,927 (96.9)	8784 (75.7)	11,642 (97)	12,747 (97.9)	14,587 (98.5)
Control group	Sex (male) (%)	664,047 (48.4)	672,892 (48.5)	678,185 (48.6)	685,327 (48.6)	690,055 (48.6)	699,135 (48.7)	702,222 (48.8)	709,721 (48.8)
	Age group (%)	145,423 (10.6)	151,512 (10.9)	156,551 (11.2)	162,965 (11.6)	171,046 (12.1)	17,9007 (12.5)	186,601 (13)	192,995 (13.3)
	Diseases (%)								
	HTN	155,816 (11.4)	161,754 (11.7)	167,511 (12)	169,014 (12)	172,013 (12.1)	173,662 (12.1)	177,452 (12.3)	182,742 (12.6)
	DM	60,570 (4.4)	64,442 (4.7)	68,583 (4.9)	70,774 (5.0)	73,578 (5.2)	76,464 (5.3)	79,755 (5.5)	85,299 (5.9)
	OVD	17,389 (1.3)	17,762 (1.3)	19,917 (1.4)	19,784 (1.4)	20,968 (1.5)	22,159 (1.5)	23,858 (1.7)	26,642 (1.8)
	CKD	3425 (0.3)	3575 (0.3)	4182 (0.3)	4815 (0.3)	5381 (0.4)	5621 (0.4)	6102 (0.4)	6909 (0.5)
	Drug (%)	1,270,089 (92.6)	1,280,028 (92.3)	1,283,945 (91.9)	1,302,754 (92.4)	897,733 (63.3)	1,322,366 (92.2)	1,322,125 (91.8)	1,346,638 (92.7)

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; OVD, other vascular diseases; SOHL, suspected ototoxicity hearing loss.
[a]The *P*-value is not statistically significant at the .05 significance level.

Table 2. Odds Ratio of Drug Prescription and Medical Diagnosis for Ototoxic Hearing Loss

	2009	2010	2011	2012	2013	2014	2015	2016
Sex								
Female					ref			
Male	1.109** (1.066, 1.154)	1.016 (0.978, 1.056)	1.037 (0.998, 1.078)	1.014 (0.976, 1.053)	1.007 (0.97, 1.046)	1.014 (0.977, 1.052)	1.016 (0.981, 1.053)	1.033 (0.999, 1.068)
Age								
<65					ref			
≥65	3.007** (2.862, 3.16)	2.927** (2.791, 3.069)	2.7** (2.572, 2.834)	2.708** (2.583, 2.839)	2.717** (2.594, 2.846)	2.763** (2.641, 2.891)	2.809** (2.691, 2.932)	3.366** (3.237, 3.501)
Diseases								
HTN								
0					ref			
1	1.319** (1.251, 1.39)	1.319** (1.254, 1.387)	1.314** (1.249, 1.382)	1.264** (1.202, 1.328)	1.324** (1.261, 1.391)	1.176** (1.12, 1.235)	1.242** (1.186, 1.3)	1.231** (1.18, 1.284)
DM								
0					ref			
1	1.423** (1.33, 1.524)	1.349** (1.263, 1.44)	1.381** (1.294, 1.473)	1.358** (1.274, 1.447)	1.229** (1.152, 1.31)	1.253** (1.178, 1.334)	1.25** (1.179, 1.325)	1.205** (1.143, 1.272)
OVD								
0					ref			
1	1.71** (1.538, 1.902)	1.661** (1.497, 1.843)	1.486** (1.338, 1.651)	1.668** (1.51, 1.843)	1.38** (1.241, 1.534)	1.634** (1.488, 1.794)	1.555** (1.423, 1.698)	1.507** (1.392, 1.632)
CKD								
0					ref			
1	1.26 (0.979, 1.622)	1.406** (1.117, 1.771)	1.425** (1.148, 1.767)	1.469** (1.209, 1.783)	1.148 (0.938, 1.405)	1.174 (0.966, 1.427)	1.173 (0.98, 1.403)	1.442** (1.252, 1.662)
Drug (use)	1.673** (1.514, 1.85)	1.771** (1.606, 1.952)	1.996** (1.804, 2.208)	2.249** (2.018, 2.508)	1.51** 1.445, 1.578)	2.366** (2.128, 2.63)	2.252** (2.042, 2.484)	2.317** (2.111, 2.543)
PPIs								
0					ref			
1	1.652** (1.57, 1.738)	1.596** (1.52, 1.675)	1.504** (1.432, 1.579)	1.622** (1.549, 1.699)	1.27** (1.145, 1.409)	1.614** (1.546, 1.686)	1.607** (1.543, 1.674)	1.523** (1.465, 1.582)
Antihistamine								
0					ref			
1	1.62** (1.521, 1.725)	1.716** (1.613, 1.825)	1.736** (1.632, 1.848)	1.888** (1.767, 2.017)	1.194** (1.147, 1.243)	1.852** (1.736, 1.975)	1.945** (1.827, 2.07)	1.835** (1.734, 1.943)
Antibiotic								
0					ref			
1	1.302** (1.232, 1.376)	1.241** (1.176, 1.309)	1.333** (1.263, 1.406)	1.357** (1.285, 1.432)	1.206** (1.154, 1.259)	1.302** (1.236, 1.371)	1.297** (1.234, 1.362)	1.217** (1.164, 1.273)
Anticancer								
0					ref			
1	0.729 (0.438, 1.215)	0.674 (0.417, 1.088)	1.104 (0.764, 1.596)	0.475** (0.28, 0.804)	1.167 (0.799, 1.703)	1.087 (0.794, 1.488)	1.084 (0.811, 1.449)	0.883 (0.584, 1.336)
Painkiller								
0					ref			
1	0.989 (0.918, 1.065)	1.016 (0.945, 1.091)	1.037 (0.966, 1.114)	1.029 (0.955, 1.108)	1.324** (1.27, 1.381)	1.002 (0.934, 1.076)	0.972 (0.909, 1.039)	1.077* (1.009, 1.15)

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; OVD, other vascular diseases; PPIs: proton pump inhibitors.
*$P < .05$ and **$P < .0001$.

Table 2 presents the OR related to medication prescriptions, gender, age, and medical history of SOHL. The risk of SOHL by gender showed an OR of 1.109 ($P < .0001$) only in 2009. The OR for the group aged ≥65 years increased from 3.007 to 3.366, indicating a higher risk compared to the group aged <65 years. The age group variable yielded statistically significant results across all years, suggesting that older individuals are more vulnerable to SOHL onset. Regarding medical history, the OR for patients with hypertension decreased from 1.319 to 1.264, and the OR for patients with diabetes also decreased from 1.423 to 1.205; however, a history of the disease remained a risk factor. For other vascular diseases and chronic kidney disease, the ORs were 1.71 to 1.507 and 1.26 to 1.442, respectively, confirming that medical history is a risk factor for SOHL.

Individuals who were prescribed any of the included medications at least once were considered to have used ototoxic drugs, with the drug use variable set to 1. The OR for this variable increased from 1.673 to 2.317, indicating that the risk of SOHL associated with medication use also increased over time. The OR for PPIs decreased from 1.652 to 1.523, and the OR for antibiotics decreased from 1.302 to 1.217; however, both still reflected a high risk. In contrast, the OR for antihistamines increased from 1.62 to 1.835, further elevating the risk of SOHL. In contrast, the OR for anticancer drugs and painkillers did not show significant effects on SOHL.

Given the strong association between drug prescriptions and age, we conducted propensity score matching (PSM) for the patient and control groups based on age, stratified by drug type, in a 1:1 ratio. Subsequently, we assessed the risk associated with each type using age-adjusted simple Cox regression and multiple Cox regression (**Figure 2**). The results from the age-adjusted simple Cox regression analysis indicated that the HR for PPIs ranged from 1.85 to 2.90, with *P*-values mostly <.0001. The HR for antihistamines ranged from 1.10 and 1.20 ($P < .0001$), confirming that their use is associated with an increased risk of SOHL. Antibiotics showed an HR ranging from 1.00 to 1.10, with statistically significant results observed only in certain years. The HR for anticancer drugs showed a notable increase in risk only in 2016. Painkillers exhibited an HR between 0.74 and 0.79, indicating a significant reduction in risk. In the age-adjusted multiple Cox regression analysis, PPIs consistently showed an HR ranging from 1.70 to 2.30 in most years ($P < .0001$), and antihistamines also showed an HR between 1.10 and 1.33 ($P < .0001$), reflecting a significant increase in risk in most years. The HR for antibiotics was 1.10, showing greater significance than in the simple regression analysis. The results for anticancer drugs and painkillers were similar to those of the age-adjusted simple Cox regression.

Additionally, the HR for SOHL diagnosis due to drug prescriptions was analyzed separately for patients aged ≥65 years and those <65 years (**Table 3**). For the group aged ≥65 years, the HR for PPIs ranged from 1.7 to 2.4, with an average HR of 1.9. The average HR for antihistamines was 1.4, indicating an increased risk of SOHL. For antibiotics, the HR varied between 1.5 and 1.6 across the years, with an average of 1.5. Anticancer drugs showed a value of 0 in some years, but high HRs of 3.8 and 6.5 were significantly observed in 2013 and 2016, respectively. Painkillers showed a low risk of 0.7 in the simple analysis. Conversely, in the group <65 years of age, the HR for PPIs increased from 1.9 to 3.4, indicating relatively high values. Antihistamines and antibiotics had average HR of 1.3 and 1.2, respectively, showing relatively lower HRs compared to the group aged ≥65 years. For anticancer drugs, a high HR of 7.7 was observed in specific situations. Painkillers also exhibited a low HR of 0.8 in this group.

Discussion

This study aimed to establish a list of drugs containing ototoxic ingredients distributed in South Korea, discover new ototoxic components, and create a unique list of ototoxic drugs for South Korea. Additionally, the drugs were grouped to assess their potential ototoxicity, which

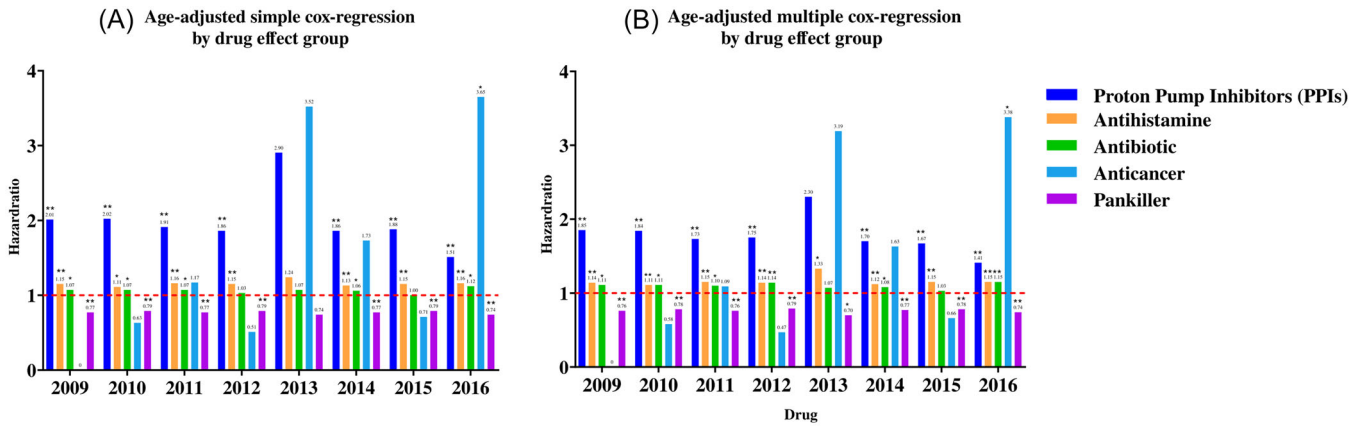

Figure 2. (A) Age-adjusted simple Cox regression by drug effect group and (B) age-adjusted multiple Cox regression by drug effect group.

Table 3. Hazard Ratios of Drug Prescription and Medical Diagnosis for Ototoxic Hearing Loss

			Simple								
Age	SOHL group		2009	2010	2011	2012	2013	2014	2015	2016	AVG
	n		499	572	587	591	63	714	813	754	
≥65	Drug										
	PPIs	0					ref				
		1	1.5*	1.6**	1.6**	1.5**	1.9	1.3*	1.3**	1.1	1.5
	Antihistamine	0					ref				
		1	1.1	1.1	1.1*	1.1	1.5*	1.1	1.1	1.1*	1.2
	Antibiotic	0					ref				
		1	1.4**	1.3**	1.3**	1.3**	1.3	1.3**	1.3**	1.4**	1.3
	Anticancer	0					ref				
		1	0.0	0.0	2.6	0.0	0.0	3.1	0.0	5.2*	1.4
	Painkiller	0					ref				
		1	0.7**	0.7**	0.7**	0.7**	0.6*	0.7**	0.7**	0.7**	0.7
	n		1471	1702	1693	1940	112	2036	2003	2070	
<65	Drug										
	PPIs	0					ref				
		1	2.0**	2.0**	1.7**	1.8**	3.4	1.9**	1.9**	1.6**	2.0
	Antihistamine	0					ref				
		1	1.2**	1.1*	1.2**	1.2**	1.2	1.1**	1.2**	1.2**	1.2
	Antibiotic	0					ref				
		1	1.0	1.1	1.0	1.0	1.0	1.0	1.0	1.1*	1.0
	Anticancer	0					ref				
		1	0.0	0.9	0.0	0.8	6.5	0.7	1.2	1.9	1.5
	Painkiller	0					ref				
		1	0.8**	0.8**	0.8**	0.8**	0.8	0.8**	0.8**	0.8**	0.8
			Multiple								
Age	SOHL group		2009	2010	2011	2012	2013	2014	2015	2016	AVG
	n		499	572	587	591	63	714	813	754	
≥65	Drug										
	PPIs	0					ref				
		1	1.9**	2.0**	2.1**	1.9**	2.4	1.7**	1.7**	1.4**	1.9
	Antihistamine	0					ref				
		1	1.3**	1.3**	1.4**	1.3**	1.7*	1.3**	1.3**	1.4**	1.4
	Antibiotic	0					ref				
		1	1.6**	1.6**	1.6**	1.5**	1.5	1.5**	1.5**	1.6**	1.6
	Anticancer	0					ref				
		1	0.0	0.0	3.3	0.0	0.0	3.8*	0.0	6.5*	1.7
	Painkiller	0					ref				
		1	-	-	-	-	-	-	-	-	
	n		1471	1702	1693	1940	112	2036	2003	2070	
<65	Drug										
	PPIs	0					ref				
		1	2.3**	2.2**	2.0**	2.1**	3.4	2.3**	2.2**	1.9**	2.3
	Antihistamine	0					ref				
		1	1.3**	1.2**	1.3**	1.3**	1.3	1.3**	1.3**	1.3**	1.3
	Antibiotic	0					ref				
		1	1.2**	1.2**	1.2**	1.1*	1.2	1.2**	1.1*	1.2**	1.2
	Anticancer	0					ref				
		1	0.0	1.1	0.0	0.9	7.7*	0.8	1.3	2.3	1.8
	Painkiller	0					ref				
		1	-	-	-	-	-	-	-	-	

Abbreviations: PPIs, proton pump inhibitors; SOHL, suspected ototoxicity hearing loss.
*$P < .05$ and **$P < .0001$.

was intended to enable clearer identification of patients with OHL and to provide a basis for clinical guidelines.

According to existing research on OHL, aminoglycoside antibiotics, painkillers, and anticancer drugs are the major causes of OHL. In particular, aminoglycoside antibiotics show a high OHL occurrence rate of approximately 63% in patients with kidney disease or severe infections. The anticancer drug cisplatin is reported to have an incidence rate exceeding 50% in adults and more than 60% in children. Additionally, furosemide, a painkiller, has been observed to cause OHL in approximately 6% to 7% of patients. The risk of OHL associated with these drugs is significantly influenced by factors such as patient age, dosage, route of administration, and comorbidities.[19]

This study also confirmed that these drugs pose a risk of SOHL, highlighting the importance of age-dependent drug prescriptions. In the group aged ≥65 years, a significant HR was observed for antibiotics, whereas in the group <65 years, anticancer drugs presented notable risks. The prescription of anticancer drugs typically aligns with the treatment cycles, suggesting that the sample used in this study may not fully reflect all treatment cycles. Furthermore, this study introduced PPIs and antihistamines, which have not been extensively studied in prior research. The literature presents conflicting findings regarding PPIs, with some studies suggesting that they can induce ototoxicity and others proposing a protective effect. The proposed mechanisms include reduced inner ear blood flow, electrolyte imbalance, cytotoxicity, drug interactions, and increased ROS levels.[9,11] The analysis based on the data in this study found evidence supporting the possibility that PPIs induce ototoxicity, particularly in patients <65 years of age, indicating a need for caution regarding potential drug misuse in younger populations. Although antihistamines are frequently used to treat patients with OHL, there is no definitive evidence that they directly induce OHL. However, the analysis revealed that patients in the SOHL group consumed more antihistamines, suggesting the need for further research into the relationship between antihistamines and ototoxicity, as well as the reasons for their use.

This study enhances the reliability of the findings by establishing a precise operational definition of OHL and utilizing big data from South Korea. Many existing OHL studies have defined ototoxic drug-induced HL based on the registration of hearing impairment, simple HL, sensorineural HL, or tinnitus.[22-24] However, such approaches may not adequately consider the detailed mechanisms and processes of OHL, potentially increasing the likelihood of errors and data omissions in the diagnostic process, thereby lowering the credibility of the research outcomes. In contrast, this study considered various HL mechanisms when defining OHL operationally. It utilized ICD-10 classification to distinguish between conductive, sensorineural, mixed, ototoxic, presbycusis, sudden, noise-induced, and other types of HL. Among these, data analysis focused on sensorineural HL and sudden HL, which directly impact the inner ear and share similar mechanisms with OHL. Patients with conductive HL, mixed HL, and presbycusis HL caused by aging were excluded from the study. By employing a more detailed operational definition, this research effectively selected patients with OHL, minimizing data omissions and enhancing the reliability of the study results.

Limitation

The HIRA-NPS data were randomly sampled each year, making it difficult to track the patients' continuous medical records.[26] As a result, only up to 1 year of medical records could be followed, which likely had a negative impact on the outcomes of anticancer medications due to insufficient consideration of the medication usage cycle. Age adjustment by TYPE was not possible in SAS for combinations of the five TYPES, and the lack of consideration for the pharmacological mechanisms of ingredients resulted in weaker outcomes for painkillers. Future research should focus on reclassifying the TYPE of medications based on their specific mechanisms of action. Additionally, this study was retrospective and could not confirm a causal relationship between medication use and HL. Future studies should utilize the entire HIRA data set to focus on factors such as duration of use and defined daily dose to establish useful medication usage guidelines. This research is expected to enhance the understanding of ototoxic mechanisms and develop strategies for preventing HL.

Conclusion

This study demonstrated that factors such as gender, age, underlying diseases, and medication use are risk factors for SOHL, providing important information for the establishment of prevention and treatment strategies. PPIs, antihistamines, antibiotics, and anticancer drugs significantly increased the risk of SOHL, whereas painkillers decreased this risk. Notably, the risk associated with PPIs and antibiotics was higher in the group aged ≥65 years, whereas the risk from PPI drugs was elevated in the group aged <65 years. This finding suggests a strong association between the use of specific drug groups and SOHL, indicating the need for caution.

Author Contributions

Jiwon Kim, conceptualization, data curation, formal analysis, investigation, methodology, resources, software, validation, visualization, writing – original draft, writing – review and editing; **Chul Young Yoon**, data curation, formal analysis, resources, software, validation, visualization; **Junhun Lee**, data curation, software, visualization; **Young Joon Seo**, conceptualization, project administration, supervision, writing – review and editing.

Disclosures

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Data Availability Statement

This study involved human participants, and the data used were managed and monitored according to strict standards. As this study used NHI data managed by the government of the Republic of Korea, researchers who wish to use these data can apply to the Health Insurance Review and Assessment Service in Korea.

Supplemental Material

Additional supporting information is available in the online version of the article.

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