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# Detection and evaluation of signals for immune-related adverse events: a nationwide, population-based study

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**Background:** Immune checkpoint inhibitors (ICIs) are one of the main pillars of cancer therapy. Since other studies such as clinical trial and retrospective study have limitations for detecting the immune-related adverse events (irAEs) characterized by unpredictable onset, nonspecific symptoms and wide clinical spectrum, we aimed to identify the incidence of irAEs and to detect and evaluate the signals using real-world data.

**Methods:** Cancer patients treated with anticancer medications were analyzed using the nationwide health insurance claims database of South Korea from 2017 to 2019, and Clinical Data Warehouse (CDW) database of Asan Medical Center (AMC), a tertiary referral hospital, from 2012 to 2019. AEs of ICI users were compared with those of non-ICI anticancer medication users. PD-1 inhibitors (nivolumab and pembrolizumab) and PD-L1 inhibitors (atezolizumab) were evaluated. We defined an AE as a newly added diagnosis after the ICI prescription using an ICD-10 diagnostic code. A signal was defined as an AE that was detected by any one of the four indices of data mining: hazard ratio (HR), proportional claims ratio (PCR), claims odds ratio (COR), or information component (IC). All detected signals were reviewed and classified into well-known or potential irAEs. Signal verification was performed for targeted AEs using CDW of AMC using diagnostic codes and text mining.

**Results:** We identified 118 significant signals related to ICI use. We detected 31 well-known irAEs, most of which were endocrine diseases and skin diseases. We also detected 33 potential irAEs related to disorders in the nervous system, eye, circulatory system, digestive system, skin and subcutaneous tissues, and bones. Especially, portal vein thrombosis and bone disorders such as osteoporosis with pathological fracture and fracture of shoulder, upper arm, femur, and lower leg showed high HR in ICI users than in non-ICI users. The signals from hospital database were verified using diagnostic codes and text mining.

**Conclusion:** This real-world data analysis demonstrated an efficient approach for signal detection and evaluation of ICI use. An effective real-world pharmacovigilance system of the nationwide claims database and the EMR could complement each other in detecting significant AE signals.

#### KEYWORDS

immune checkpoint inhibitor, immune-related adverse event, drug safety surveillance, pharmacovigilance, data mining

## **1** Introduction

Immune checkpoint inhibitors (ICIs), which activates the immune system to fight against cancer, have evolutionally changed the recent trend of cancer therapy. Monoclonal antibodies targeting T-cell immune checkpoint molecules, including programmed cell death protein 1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T lymphocyte associated protein-4 (CTLA-4), are the most effective examples of ICIs. Randomized clinical trials involving ICIs have demonstrated the durable clinical benefits of these medications across a diverse range of cancers (1–3).

However, patients treated with ICI may experience immunerelated adverse events (irAEs), which are autoimmune disease-like toxicities caused by immune reaction associated with this treatment. These events exhibit distinct characteristics compared to those observed with conventional cytotoxic chemotherapy or targeted agents. They can affect any part of the body with diverse severity and onset times (4, 5). The unique profile of irAEs, characterized by unpredictable onset, even after the completion of treatment, nonspecific symptoms, a broad clinical spectrum, and in some cases, irreversibility and fatality poses a significant challenge in the pharmacovigilance of ICIs. Clinical trials have reported various adverse events (AEs), but they have limitations since they collect data from a limited number of selected populations for a restricted duration of time. In particular, ICIs have often received accelerated approval from regulatory agencies based on results from earlier phase studies with small samples sizes and short study durations (6, 7). This may increase the risk of the AEs not being fully characterized in pre-marketing clinical trials. Therefore, postmarketing pharmacovigilance of ICIs is particularly crucial to capture real-world experiences. Several efforts have been undertaken to identify AE signals using post-market pharmacovigilance databases (8-13). However, these databases primarily consist of voluntary AE reports, making them susceptible to various reporting biases and rendering them inadequate for calculating AE incidence. Large-scale observational studies using real-world data, such as electronic health records, medical claims and billing data, and registries, have the potential to overcome the inherent limitations of clinical trials and spontaneous reporting databases. Given that the National Health Insurance (NHI) system in South Korea provides healthcare coverage to the entire population residing the country and that all reimbursing claims with diagnostic codes are evaluated by the Health Insurance Review and Assessment Service (HIRA), the claim data of HIRA can be considered an appropriate data source for pharmacovigilance research. Several attempts have been made to utilize health insurance claims data as a pharmacovigilance tool for conducting post-marketing surveillance, employing multiple data mining methods (14, 15).

In the present study, our objective was to monitor known irAEs in a real-world setting and identify potential new AE signals in patients undergoing treatment with ICIs. To achieve this, we utilized a nationwide, population-based claim database as a primary data source and further validated these signals using a clinical data warehouse.

## 2 Methods

### 2.1 Data source for signal detection

We defined the potential risk associated with ICI usage as a "signal", a term frequently used in pharmacovigilance. This term denotes "Information originating from one or several sources, indicating a possible new causal relationship or a novel aspect of a known association between an intervention and an event or a group of related events, whether adverse or beneficial" (16, 17). Signal detection in this study was conducted using the HIRA database. The HIRA database includes all information on approximately 50 million people, the whole Korean population covered by the NHI program since 2000. Every resident in South Korea is provided with a unique civil registration number. The NHI program provides coverage for all residents in a form of compulsory social insurance, which ensured the complete follow-up of study participants. In South Korea, the NHI system started to reimburse ICI treatment for non-small cell lung cancer (NSCLC) and bladder cancer from August 2017, and for melanoma from February 2018 (18). We obtained the claims data of patients with NSCLC, melanoma, and bladder cancer that had been submitted by healthcare providers between January 1, 2014, and January 31, 2019, with anonymized identifiers provided by the HIRA to protect their privacy, in accordance with the Act on the Protection of Personal Information Maintained by Public Agencies. The database contains information on demographic records, diagnosis, procedures performed, and prescriptions. Demographic information included age and sex. All diagnoses were coded using the Korean Standard Classification of Disease, seventh edition (KCD-7), a modified version of the International Classification of Disease and Related Health Problems, 10th revision (ICD-10). The prescription data included generic name of the drug according to the HIRA drug formulary code, prescription date, and duration. Access to the HIRA database was limited to researchers who completed an application process and were granted approval for research access.

#### 2.2 Ethics

This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2019-1300, 2019-1247), and informed consent was waived.

## 2.3 Study subjects for signal detection

In this study, we retrospectively identified patients with NSCLC, bladder cancer, and melanoma by using the KCD-7 codes for primary and secondary diagnoses (C34, C67, and C43, respectively), as well as the corresponding cancer-specific deductible insurance codes (V027 for NSCLC, V193 for bladder cancer, and V194 for melanoma). These patients were then categorized into two groups: the ICI group and the non-ICI group. Utilizing the 5-year HIRA claims database (from January 1, 2014, to January 31, 2019), we selected patients who received anticancer medication between August 2017 and January 2019, based on the initiation date (August 2017) of the NHI coverage for ICIs. The ICI group consisted of patients who received at least one cycle of treatment with PD-1 inhibitors (nivolumab and pembrolizumab) or PD-L1 inhibitor (atezolizumab) inhibitor between August 2017 and January 2019. The non-ICI group, serving as the comparator, included patients who received non-ICI systemic anticancer agents such as cytotoxic chemotherapy and molecular targeted therapy (Supplementary Table S1) for NSCLC, bladder cancer, and melanoma during the same period as the ICI group. The index date for each patient was defined as the first prescription date of the corresponding drug, and all study patients were followed up for a maximum of 18 months from the index date. AEs in the ICI group were compared with those in the non-ICI anticancer medication group.

## 2.4 Definition of adverse events

In this study, AEs were identified from the claims study database by considering newly added diagnosis codes during treatment. AEs were defined as diagnoses that did not exist prior to exposure to the drug of interest but were added after exposure. The KCD-7 coding system, which consists of 21 chapters with various code blocks, was used for classification. Physicians in South Korea are required to report the most specific diagnosis code available according to the KCD-7 coding system, ranging from three to seven digits, in the medical care cost statements submitted to the NHI system.

Initially, a low-level classification was performed using threedigit KCD codes, resulting in a group of 1,348 codes. Subsequently, a mid-level classification was conducted using groups of three-digit KCD codes to categorize single conditions within each block, resulting in a total of 222 codes. However, certain disease categories were excluded from the study. The neoplasm category (KCD-7 codes, C00-D48) was excluded due to the difficulty in distinguishing it from existing cancers, which are already indications for ICIs. Additionally, pregnancy-related diagnosis including "Pregnancy, childbirth, and the puerperium" (O00-O99), "Certain conditions originating in the perinatal period" (P00-P96), and "Congenital malformations, deformations, and chromosomal abnormalities" (Q00-Q99) were excluded to focus on non-pregnant cancer patients.

#### 2.5 Signal detection criteria

The hazard ratio (HR) was computed by dividing the incidence of ICI-specific AE pairs (A) by the total observed duration of claims (T<sub>1</sub>), and then dividing the results by the incidence of non-ICI-AE pairs (C) divided by the total observed duration of claims (T<sub>0</sub>). If the lower limit of the 95% confidence interval (CI) of an AE's HR was greater than 1, it was considered a potential signal possibly associated with ICIs.

Disproportionality measures were also employed to detect AE signals, using proportional claims ratios (PCRs), claims odds ratios (CORs), and Bayesian confidence propagation neural networks (BCPNNs) of information components (ICs). These measures were specifically adapted for use with the claims database, as opposed to spontaneous reporting databases. Two-by-two tables were constructed, combining the frequency of drug–AE pairs and total claims, along with the estimated indices for each AE (Table 1).

PCR is defined as the ratio between the incidence of a specific AE associated with a particular ICI and the incidence of AEs related to non-ICI drugs listed in the database (19). COR represents the odds ratio of developing a specific AE compared to all other events for the ICI group compared with the odds of developing AEs when using non-ICI drugs listed in the database (18, 19). A signal was deemed significant if the lower limit of the 95% CIs for PCR or COR

TABLE 1 Study framework of the disproportionality analysis of the health insurance claims database.

Drug exposure	Specific AE	Non-specific AE	Total claims time
ICI	А	В	$T_1$
Non-ICI	С	D	T <sub>0</sub>

AE, adverse event; ICI, immune checkpoint inhibitors.

was greater than 1, or if the number of ICI-specific AE pairs (A) was equal to or greater than 3. For the BCPNN analysis, a signal was considered statistically significant if the lower limit of 95% credible interval was above 0 (20) (Table 2).

In this study, any AE that was detected by at least one of the four indices (HR, PCR, COR, and IC) was considered a signal. The statistical analyses were conducted using SAS Enterprise Guide (version 7.1; SAS institute, NC, USA) and R version 3.6.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Significant signals only in the ICI group compared to the non-ICI group were presented.

### 2.6 Signal categorization

The detected AEs from the HIRA database were reviewed independently by two medical oncologists. They assessed the expectedness and frequency of the AEs compared to previous literature (21, 22). The detected AEs were categorized based on the following conditions: 1) Well-known irAEs that were established as related to immunotherapy based on previous literature, and/or are associated with the pathogenesis of the disease entity involving autoimmune activation; 2) potential irAEs that were not previously recognized as irAEs, but were considered clinically relevant and important.

## 2.7 Signal verification

Signal verification was conducted using the Clinical Data Warehouse database of Asan Medical Center (AMC) to validate targeted AEs. This validation involved utilizing diagnostic codes and text mining techniques. Recognizing the limitation of the HIRA database, which relies on health insurance claims data, the electronic medical record (EMR) from the tertiary care hospital, AMC, was employed to verify targeted AEs based on symptoms or laboratory abnormalities. The research team, consisting of clinical experts, reviewed and discussed the detected signals to choose the targeted AEs. Access to the CDW database is restricted to inhospital researchers who have received approval from both the Institutional Review Board and the Data Subcommittee.

TABLE 2 Definition and signal detection criterion for data mining indices.

Indices	Definition	Detection criterion
Hazard ratio	$(A/T_1)/(C/T_0)$	Lower limit of 95% CI>1, A≥3
Proportional claims ratio	{A/(A+B)}/{C/(C+D)}	Lower limit of 95% CI>1, A $\geq$ 3
Claims odds ratio	(A/B)/(C/D)	Lower limit of 95% CI>1, A≥3
Information component	log <sub>2</sub> P(AE, Drug)/P (AE)P(Drug)	Lower limit of 95% credible interval≥0, A, C≥1

CI, confidence interval; P, probability. See Table 1 for what A, B, C, and D mean. Among 21,205 cancer patients diagnosed with NSCLC, melanoma, or bladder cancer between July 1, 2012 and January 31, 2019 from the hospital EMR database, 9236 patients who received systemic anticancer therapy were identified using diagnostic and prescription codes (Supplementary Figure S1). These patients were classified into two groups: ICI users (n=836) and non-ICI users (n=8,400). The observation period for all participants commenced from their respective first prescription date, and they were followed up until the end of the study period.

In addition, we identified the other validation group of 1,706 ICI users from the hospital EMR database, comprising patients diagnosed with any type of cancer, for clinical text analysis (text mining). This validation group included patients who were not reimbursed for ICI treatment. Then, these 1,706 ICI users were matched in a 1:2 ratio to 3,412 non-ICI users based on age, sex, and cancer subtype to compare the detailed information documented in the narrative chart.

Among the detected AE signals, targeted AEs that could be easily detected using diagnostic codes or diagnostic codes required on prescriptions were searched using the diagnostic code information ('diagnostic code from the hospital EMR data', n=9236). On the other hand, text mining techniques were applied to search for targeted AE signals that could be easily detected in narrative EMR records such as nursing records and progression notes ('text mining applied to the hospital EMR data', n=5118; 1,706 ICI users and 3,412 non-ICI users). Thus, there were not only signals that were verified by both methods, but also other signals excluded from each analysis.

To explore the unstructured data obtained from the EMR, including the clinical notes written by medical staff, we utilized Standard Query Language with the LIKE function in the R package (SQLDF) to identify meaningful words. The operational definition of the verified signals, including the disease category and detailed search terms, can be found in Supplementary Table S2.

## **3** Results

### 3.1 Characteristics of the study subjects

A total of 314,423 patients were diagnosed with NSCLC, melanoma, or bladder cancer between July 2014 and January 2019. Among these patients, 25,817 were prescribed with anticancer medications from August 2017 to January 2019. Among them, 4,516 patients received ICIs, while 21,301 patients received non-ICI anticancer medications (Supplementary Figure S2).

Baseline characteristics of the study patients are shown in Supplementary Table S3. While there were statistically significant differences between the ICI group and the non-ICI group in all variables, the differences were not clinically significant. Overall, 74.1% of the patients were male, with a mean ( $\pm$  standard deviation; SD) age of 66.4 ( $\pm$  10.0) years and a mean ( $\pm$  SD) Charlson comorbidity index (CCI) of 7.5 ( $\pm$  3.6). The majority of patients had NSCLC (88.5%), while bladder cancer and melanoma accounted for 9.0% and 2.6% of the cases, respectively. In the ICI group, 75.6% of the patients were male, with a mean ( $\pm$  SD) age of 64.9 ( $\pm$  10.0) years and a mean ( $\pm$  SD) CCI of 8.6 ( $\pm$  3.6). The majority of patients in this group had NSCLC (83.1%), while bladder cancer and melanoma accounted for 11.4% and 5.6% of the cases, respectively.

# 3.2 Number of detected signals from the National Health Insurance claims database

Figure 1 illustrated the number of detected signals and the logical relations in which the detection criterion was satisfied by each index. Out of the 1,570 screened AEs using the KCD code, a total of 118 distinct AEs were identified as signals associated with ICIs using the HR index (n=115), PCR index (n=67), COR index (n=49), and IC index (n=43). The HR index demonstrated the highest number of detections, followed by PCR, COR, and IC, in descending order.

## 3.3 Detected AE signals

#### 3.3.1 Incidence of detected AE signals

When detected AEs were categorized by the organ system, the ICI group exhibited the highest incidence of AEs in the endocrine, respiratory, dermatologic, and musculoskeletal systems, which included disorders in the thyroid gland (E00–E07, 20.8%), other disorders of the thyroid gland (E07, 16.0%), influenza and pneumonia (J09–J18, 21.1%), pneumonia, (J18, 18.6%), pruritus, (L29, 11.4%), and arthropathies (M00–25, 17.5%) (Table 3; Supplementary Table S4). Mental and behavioral disorders (F00–99) as well as infectious and parasitic diseases (A00–B39) were also

common AEs observed in the ICI group, ranging from 5% to 10% in incidence. Hepatic organ-related AEs (K71) were present in approximately 4% of the ICI group. Other AEs, such as neurologic (G00–99), circulatory (I00–99), and digestive diseases (K00–93), were relatively infrequent, with an incidence of less than <5%. The Table 3 displays 43 AE signals that were found to be significant in all four criteria (HR, PCR, COR, IC) among the 118 detected signals of AEs associated with the use of ICIs in the HIRA database. These signals met the threshold for significance across all four indices, indicating a strong association with ICI treatment.

#### 3.3.2 Well-known immune-related AEs

Well-known irAEs were identified in endocrine and skin diseases in association with the use of ICIs (Figure 2A). The incidence of endocrine diseases was significantly higher in patients receiving ICIs, including endocrine gland disorders (HR: 5.5, 95% CI: 3.2-9.7), other types of hypothyroidism (HR: 4.4, 95% CI: 3.7-5.2), disorders of the thyroid gland (HR: 4.0, 95% CI: 3.6-4.4), and other disorders of the thyroid (HR: 3.8, 95% CI: 3.4-4.2). Furthermore, the use of ICIs was strongly associated with skin disease, such as vitiligo (HR: 17.7, 95% CI: 5.7-54.8), lichen planus (HR: 11.5, 95% CI: 2.9-46.0), and erythema multiforme (HR: 5.6, 95% CI: 2.3-13.4). In addition, as is well known, connected tissue disorders, including systemic lupus erythematosus (HR: 4.9, 95% CI: 1.7-4.9) and other systemic involvement of connective tissue (HR: 2.8, 95% CI: 1.5-2.8), as well as and nervous disease such as nerve, nerve root, and plexus disorders (HR: 1.3, 95% CI: 1.1-1.6), were detected with a significant association with ICI use.

### 3.3.3 Potential ICI-related AE

Detected AEs that were not previously well-known but judged as clinically relevant and important were defined as potential ICI-



Number of detected signals related to immune checkpoint inhibitor use by data-mining indices in the nationwide claims database. HR, hazard ratio; PCR, proportional claims ratio; COR, claims odds ratio; IC, information component; KCD, Korean Standard Classification of Diseases. \* means number of detected signals in mid-level.

TABLE 3 Adverse event signals significant in all four criteria (HR, PCR, COR, IC) in the HIRA database.

	KCD	Fuelish	ICI	user	N ICI	on- -user		HR			PCR			COR		IC**
	code	de Engusin	AE (%)	Total	AE (%)	Total	point estimates	lower Cl	upper Cl	point estimates	lower CI	upper Cl	point estimates	lower Cl	upper Cl	
IV. E	Indocrine	e, nutritional and metabolic diseas	es (E00	0-E90)												
W*	E00- E07	Disorders of the thyroid gland	20.8	2,784	7.6	14,323	3.96	3.58	4.38	2.73	2.52	2.94	3.18	2.85	3.55	0.94
W	E03	Other types of hypothyroidism	5.9	4,068	1.7	19,313	4.38	3.71	5.17	3.4	3.08	3.76	3.55	3	4.21	1.04
W	E05	Thyrotoxicosis [hyperthyroidism]	1.4	4,344	0.5	20,454	3.1	2.26	4.25	2.57	2.09	3.15	2.59	1.89	3.55	0.59
W	E06	Thyroiditis	1	4,409	0.4	20,742	3.34	2.31	4.82	2.71	2.15	3.43	2.73	1.89	3.95	0.58
W	E07	Other disorders of thyroid	16	3,280	5.8	16,884	3.8	3.42	4.23	2.77	2.56	2.99	3.11	2.77	3.48	0.95
	E20– E35	Disorders of other endocrine glands	3.7	4,224	2.6	20,126	1.69	1.41	2.02	1.39	1.21	1.6	1.41	1.17	1.69	0.13
P*	E24	Cushing's syndrome	0.1	4,509	0	21,262	5.74	1.66	19.85	4.72	2.54	8.77	4.72	1.37	16.31	0.18
	E27	Other disorders of the adrenal gland	2.2	4,363	1.5	20,945	1.79	1.42	2.24	1.49	1.25	1.77	1.5	1.19	1.89	0.14
	E35	Disorders of the endocrine glands in diseases classified elsewhere	0.5	4,501	0.1	21,196	5.54	3.16	9.71	4.52	3.39	6.02	4.54	2.59	7.96	0.81
Р	E83	Disorders of mineral metabolism	4.5	4,191	3.4	20,206	1.58	1.34	1.86	1.33	1.17	1.51	1.34	1.14	1.58	0.1
V. M	lental and	d behavioral disorders (F00-F99)														
Р	F05	Delirium, not induced by alcohol and other psychoactive substances	3.9	4,409	3.2	21,017	1.48	1.25	1.75	1.23	1.08	1.41	1.24	1.05	1.47	0.01
VI. [	Diseases o	of the nervous system (G00-G99)														
Р	G40	Epilepsy	3.8	4,107	3	20,088	1.58	1.33	1.88	1.29	1.12	1.49	1.3	1.09	1.56	0.05
	G80– G83	Cerebral palsy and other paralytic syndromes	2.2	4,362	1.5	20,811	1.77	1.4	2.22	1.46	1.22	1.74	1.47	1.17	1.85	0.12
	G81	Hemiplegia	1.6	4,420	1	20,971	1.94	1.47	2.55	1.6	1.31	1.97	1.61	1.23	2.13	0.16
	G83	Other paralytic syndromes	0.3	4,482	0.1	21,187	2.65	1.34	5.26	2.18	1.37	3.49	2.18	1.1	4.33	0.01
	G93	Other disorders of the brain	0.8	4,449	0.5	21,015	1.93	1.32	2.83	1.59	1.19	2.12	1.59	1.09	2.34	0.02
VII.	Diseases	of the eye and adnexa (H00-H59)														
Р	H28	Cataract and other disorders of lens in diseases classified elsewhere	0.1	4,514	0	21,256	5.82	1.45	23.27	4.71	2.35	9.42	4.71	1.18	18.85	0.06
															((	Continued)

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#### TABLE 3 Continued

	KCD	Frankala	ICI	user	N ICI	lon- -user		HR			PCR			COR		IC**
	code	English	AE (%)	Total	AE (%)	Total	point estimates	lower Cl	upper Cl	point estimates	lower Cl	upper Cl	point estimates	lower Cl	upper Cl	
						IX.	Diseases of the ci	rculatory sys	stem (100-199	)						
Р	I46	Cardiac arrest	4.4	4,490	2.7	21,243	1.97	1.67	2.31	1.64	1.45	1.85	1.67	1.41	1.97	0.33
Р	I81	Portal vein thrombosis	0.1	4,515	0	21,291	5.57	1.79	17.28	4.72	2.68	8.31	4.72	1.52	14.64	0.27
X. E	iseases c	of the respiratory system (J00-J99	))													
	J90– J94	Other diseases of pleura	9.3	3,501	7.1	17,681	1.53	1.36	1.73	1.3	1.17	1.43	1.33	1.17	1.51	0.13
w	J90	Pleural effusion, NEC	7.2	3,706	5.5	18,540	1.55	1.35	1.77	1.3	1.17	1.46	1.33	1.15	1.53	0.12
	J91	Pleural effusion in conditions classified elsewhere	1.9	4,369	1.3	20,865	1.72	1.34	2.21	1.45	1.19	1.76	1.46	1.13	1.87	0.08
XI.	Diseases	of the digestive system (K00-K93)														
	K87	Disorders of gallbladder, biliary tract, and pancreas in diseases classified elsewhere	0.4	4,494	0.1	21,253	5.34	2.75	10.37	4.47	3.17	6.29	4.48	2.31	8.70	0.68
XII	Diseases	of the skin and subcutaneous tiss	ue (LOC	)-L99)												
w	L43	Lichen planus	0.1	4,501	0	21,245	11.48	2.87	45.95	9.44	5.94	14.99	9.45	2.36	37.81	0.58
w	L51	Erythema multiforme	0.2	4,497	0	21,249	5.57	2.32	13.39	4.73	3.05	7.33	4.73	1.97	11.38	0.51
Р	L74	Eccrine sweat disorders	0.1	4,506	0	21,239	5.7	1.65	19.71	4.71	2.53	8.77	4.72	1.37	16.30	0.17
	L80– L99	Other disorders of the skin and subcutaneous tissue	11	3,633	8.3	18,038	1.58	1.42	1.77	1.33	1.21	1.46	1.37	1.22	1.54	0.17
w	L80	Vitiligo	0.3	4,484	0	21,212	17.66	5.69	54.79	14.19	10.68	18.86	14.23	4.59	44.13	1.07
Р	L89	Decubitus ulcer and pressure area	8.8	4,305	6.2	20,806	1.68	1.5	1.88	1.41	1.29	1.55	1.45	1.29	1.63	0.23
XIII	Diseases	s of the musculoskeletal system ar	nd con	nective t	issue (l	M00-M99	))	1								
	M30- M36	Systemic connective tissue disorders	0.5	4,439	0.3	20,965	2.39	1.47	3.89	1.94	1.37	2.74	1.94	1.2	3.16	0.11
w	M32	Systemic lupus erythematosus	0.1	4,502	0	21,219	4.92	1.65	14.65	4.04	2.24	7.27	4.04	1.36	12.04	0.18
w	M35	Other systemic involvement of connective tissue	0.4	4,463	0.2	21,090	2.77	1.53	5.01	2.22	1.48	3.33	2.23	1.23	4.04	0.12

(Continued)

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	KCD	English	ICI	user	N ICI	on- -user		HR			PCR			COR		IC**
	code	Engusti	AE (%)	Total	AE (%)	Total	point estimates	lower Cl	upper Cl	point estimates	lower Cl	upper Cl	point estimates	lower Cl	upper Cl	
Р	M84	Disorders of continuity of bone	0.9	4,454	0.5	21,148	2.16	1.49	3.13	1.77	1.35	2.32	1.78	1.22	2.58	0.15
XVI	II. Sympto	oms, signs and abnormal clinical a	nd lab	oratory fi	indings	, not else	ewhere classif	ied (R00-F	(99)							
	R18	Ascites	1.4	4,454	0.9	21,095	1.88	1.41	2.51	1.56	1.25	1.94	1.57	1.17	2.10	0.11
	R44	Other symptoms and signs involving general sensations and perceptions	0.1	4,502	0	21,264	5.89	1.88	18.42	4.72	2.68	8.32	4.73	1.52	14.67	0.27
	R95– R99	Ill-defined and unknown causes of mortality	0.6	4,514	0.3	21,297	2.4	1.53	3.77	1.99	1.45	2.73	2	1.27	3.13	0.18
	R99	Other ill-defined and unspecified causes of mortality	0.5	4,514	0.3	21,297	2.48	1.53	4.01	2.06	1.47	2.88	2.06	1.28	3.34	0.17
XIX	. Injury, p	oisoning and certain other consec	quence	s of exte	rnal ca	uses (SO	0-T98)									
Р	\$32	Fracture of the lumbar spine and pelvis	1.6	4,343	1	20,523	1.97	1.51	2.58	1.59	1.3	1.95	1.6	1.22	2.10	0.16
Р	S42	Fracture of the shoulder and upper arm	0.4	4,463	0.2	21,124	2.62	1.48	4.65	2.12	1.43	3.15	2.12	1.2	3.76	0.1
	S70- S79	Injuries to the hip and thigh	1.7	4,152	1.2	19,599	1.8	1.38	2.35	1.48	1.2	1.81	1.48	1.13	1.94	0.08
	S70	Superficial injury of the hip and thigh	0.7	4,393	0.3	20,702	2.34	1.52	3.61	1.92	1.41	2.62	1.93	1.25	2.98	0.16
Р	S72	Fracture of the femur	0.7	4,460	0.4	21,075	2.21	1.45	3.36	1.82	1.34	2.47	1.82	1.2	2.78	0.11
XX.	External	causes of morbidity and mortality	(V01-)	(98)												
	X50- X57	Overexertion, travel, and privation	0.1	4,515	0	21,295	16.98	1.76	163.40	14.15	8.03	24.93	14.16	1.47	136.15	0.26

\*W is for Well-known immune-related AEs (dark shade), and P is for Potential ICI-related AEs (light shade).

 $\ast\ast$  The IC value is statistically significant when it is greater than zero.

KCD, Korean Standard Classification of Diseases; AE, adverse events; HR, hazard ratio; CI, confidence interval; PCR, proportional claims ratio; COR, claims odds ratio; IC, information component lower credible interval, NEC; not elsewhere classified.

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Construction, number land metabolic diseases (200-EN)         Construction         Co	Code	Disease categories	ici Ae %	Non- AE %		R(95% CI)			HR sig.	PCR sig.	COR sig.	IC sig.
Code       Discrete projection projection (CoD-DP)       Code       Projection (Code DP)       Projection (	E00 507	IV. Endocrine, nutritional and metabolic diseases (E00-E90)	20.0	70		0 (2 6 4 4)				*	*	
E33       Option hypothymolity hypothymolypo	E00-E07	Subclinical iodine-deficiency hypothyroidism	20.8	0.1	4.	0 (3.0-4.4) 8 (1.2-6.6)		-		*	*	
EDS       Tryrestocicallymethyracitang       1.4       0.5       3.12       1.4       1.4       1.5       1.4       1.4       1.5       1.4       1.4       1.5       1.4       1.4       1.5       1.4       1.4       1.5       1.4       1.4       1.5       1.4	E03	Other hypothyroidism	5.9	1.7	4.	4 (3.7-5.2)			•	*	*	
EVEY         Other Structure         Iso         Value	E05	Thyrotoxicosis[hyperthyroidism]	1.4	0.5	3.	1 (2.3-4.2)	_	•	*	*	*	*
Clock of black of the reverse system (Cob-Cs) of the construction of the constructi	E06 E07	Other disorders of thyroid	1.0 16	0.4 5.8	3.	3 (2.3-4.8) 8 (3.4-4.2)		-		*	*	
M. Decases of the moreous system (000-099)         0.0         3.3         0.10         3.3         0.10         0.0 <th0.0< th="">         0.0</th0.0<>	E10-E14	Diabetes mellitus	10.7	10.5	1.	2 (1.1-1.4)	-		*			
Color         Dimensional cuiso during and unspective classes         U II         U III         U IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	0.05	VI. Diseases of the nervous system (G00-G99)	. ·	0.5	_	, , , ,		_				
Control       Present norw consistent intractions       03       02       12       1410-040         Control       Decision of myoconal junction and muscles       03       02       12       14	G03	Meningitis due to other and unspecified causes	0.1 3.6	0.0	3.	3 (U.8-13.7) 3 (1 1-1 6)	-#-	-	•	-		
G33       Cancel in more disorders in disease classing disease (biology)       20       1.8       1.4 (11-1.6)         F00       Cancel in more disorders (biology)       3       0.2       1.9 (0.3.4)         F10       More present dimension       7.8       8.8       1.2 (11-1.6)         F10       Presentation operation dimension       7.8       8.8       1.2 (11-1.6)         F10       Presentation operation operation operation operation       7.8       8.8       1.2 (11-1.6)         F11       Presentation operation operation operation       7.8       9.8       1.3 (11-1.6)         F11       Presentation operation operation operation       7.8       9.8       1.3 (11-1.6)         F11       Presentation operation operation operation       7.8       9.8       1.3 (11-1.6)         F11       Presentation operation operation       7.8       9.8       1.3 (11-1.6)       + </td <td>G51</td> <td>Facial nerve disorders</td> <td>0.3</td> <td>0.2</td> <td>1.</td> <td>9 (1.0-3.6)</td> <td>-</td> <td>_</td> <td>*</td> <td></td> <td></td> <td></td>	G51	Facial nerve disorders	0.3	0.2	1.	9 (1.0-3.6)	-	_	*			
GT0-GT3       Diseases of the space induces (M0-29)       0.3       0.2       1.9       2.19       (10-34)         M2       Designess of the space induces (M0-29)       0.3       0.2       1.9       (10-34)         M3       Presentation a construction (M0-29)       0.3       0.2       1.9       (10-34)         M3       Presentation (Construction and muscle)       0.2       0.1       2.7       (11-45)         M3       Presentation (Construction and muscle)       0.2       0.1       2.7       (11-45)         M3       Presentation (Construction and muscle)       0.4       0.3       0.1       1.2       1.1       1.1       1.2       1.1       1.1       1.2       1.1       1.1       1.1       1.2       1.1       1.1       1.1       1.1       1.1       1.2       1.1       1.2       1.1       1.2       1.1       1.1       1.1	G53	Cranial nerve disorders in diseases classified elsewhere	2.0	1.8	1.	4 (1.1-1.8)		_	•			
H20       With screening       0.3       0.2       19 (10-3.4)         H21       With screening       0.3       0.2       19 (10-3.4)         H23       Preservois, organism unspecified       16.6       18.8       12 (11-1.3)         H23       Preservois, organism unspecified       12.6       18.8       12 (11-1.3)       •       ·       ·       ·         H23       Preservois, organism unspecified       12.3       13 (11-1.6)       •       · </td <td>G70-G73</td> <td>Diseases of myoneural junction and muscle</td> <td>0.2</td> <td>0.1</td> <td>2.</td> <td>7 (1.1-6.6)</td> <td></td> <td></td> <td>×</td> <td>*</td> <td></td> <td></td>	G70-G73	Diseases of myoneural junction and muscle	0.2	0.1	2.	7 (1.1-6.6)			×	*		
Code         Discusso of the respiratory system (ROD-Og)	H20	VII. Diseases of the eye and adnexa (H00-H59)	03	0.2	1	9 (1 0-3 4)		_				
138       Preumonia, organization unspecified       116       18.8       12 (11-13)         139       Preumonia, organization unspecified       12       2 (11-13)       •         130       Preumonia, organization unspecified       12       2 (11-13)       •         131       Preumonia, organization unspecified       13 (11-14)       •       •         131       11-145       •       •       •       •         132       Adaptic offensities       13 (11-145)       •       •       •         133       13 (11-145)       •       •       •       •       •         133       13 (11-145)       •       •       •       •       •       •         134       Preumonia (and anot ubocutaneous tissue (ROA-139)       14 (12-17)       •	1120	X. Diseases of the respiratory system (J00-J99)	0.5	0.2		3 (1.0-3.4)						
Job Pearal affasion, NECC:       72       2.5       1.5 (1.4.1.5)         K1 Discusse of the dispates of t	J18	Pneumonia, organism unspecified	18.6	18.8	1.	2 (1.1-1.3)	-		*			
Code       12 Intervent and information exclusions (LOP-L99)       2.0       2.1       1.9 (1,1-1/2)         Chronic hegalitis, NLCC       3.2       3.0       1.3 (1,1-1.6)       •       •         L33       Allengic contract demantia       7.7       7.8       1.2 (1,0-1.4)       •       •         L34       Allengic contract demantia       7.7       7.8       1.2 (1,0-1.4)       •       •         L34       Allengic contract demantia       7.7       7.8       1.2 (1,0-1.4)       •       •         L34       Allengic contract demantia       1.0       1.0       1.1 (1,0.1.3)       •       •       •         L34       Proublesquame disorders       1.1       0.0       1.4 (1,0-1.3)       •       •       •       •         L35       Utilized from musclookeka system and connective task (Mode 49)       0.1 (7.4,7.4,7.4)       •	J90	Pleural effusion, NEC	7.2 2.5	5.5	1.	5 (1.4-1.8)			*	*	*	•
Kr1       Toxic Theoret disease and subcrates (Lob 9)       4.0       3.7       1.3 (1.1-1.5)         Chroch heartis, NEC       3.2       3.0       1.3 (1.1-1.6) <ul> <li>Image: Chroch heartis, NEC</li> <li>Image: NEC</li> <li>Image: Chroch heartis, NEC</li> <li>Image: NEC</li> <li>Image: NEC</li> <li>Image: NEC&lt;</li></ul>	190	Respiratory failure, NEC X I. Diseases of the digestive system (K00-K93)	∠.5	∠.1	1.	4 (1.1-1.7)						
K173       Chronic hegalitis, NEC       32       30       1.3 (1.1.1.6)         VIII. Descendent of the state in and subclataneous tissue (0.04.99)       50       1.4 (1.1.6)       -         L23       Managic contains       1.7       7.8       1.3 (1.1.1.6)       -         L24       Unspecific on the state in and subclataneous tissue (0.04.99)       1.1       1.3 (1.1.1.6)       -       -         L24       Unspecific on the state in and subclataneous tissue (0.04.99)       1.1       1.1       1.2 (1.1.6)       -       -         L29       Prunking time in anoma printing       0.2       0.0       1.7 (7.6.7.4.9)       -       -       -         L20       High printing       0.1       0.2       0.1       1.7 (7.6.7.4.9)       - <td>K71</td> <td>Toxic liver disease</td> <td>4.0</td> <td>3.7</td> <td>1.</td> <td>3 (1.1-1.5)</td> <td></td> <td></td> <td>*</td> <td></td> <td></td> <td></td>	K71	Toxic liver disease	4.0	3.7	1.	3 (1.1-1.5)			*			
Low Anti-contrains         Anti-contrains         Anti-contrains         Anti-contrains         Anti-contrains           123         Anti-contrains         14	K73	Chronic hepatitis, NEC	3.2	3.0	1.	3 (1.1-1.6)	-		•			
123       The process method is and paragine of the method is a substances taken internality       3.0       2.7       7.8       1.2 <t< td=""><td>1.20</td><td>X II. Diseases of the skin and subcutaneous tissue (L00-L99)</td><td>4.6</td><td>30</td><td>4</td><td>4 (1 2-1 7)</td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	1.20	X II. Diseases of the skin and subcutaneous tissue (L00-L99)	4.6	30	4	4 (1 2-1 7)						
L25       Unspecified contact demaitis       1.0       1.7       1.2       1.4	L23	Allergic contact dermatitis	7.7	7.8	1.	2 (1.0-1.4)						
L27 Laboratis due to substances taken internally and provide provide and provide provide and provide the substances theorem in the provide and provide the provide provide and provide the substances of the provide and provide an	L25	Unspecified contact dermatitis	1.9	1.7	1.	4 (1.1-1.8)				•		
Loss but in any control for an purgo         2.5         2.1         1 <th1< th="">         1         <th1< th="">         1</th1<></th1<>	L27	Dermatitis due to substances taken internally	3.0	2.7	1.	3 (1.1-1.6)	-		*			
Light 43       Light planes       11       0.0       11/1 (0.16)         List       Explore planes       0.1       0.0       15/1 (2.9.46,0)         List       Explore muscubstetical system and connective lass (PRO-M99)       0.0       4.2 (1.7.47, 1.7.5, 7.8, 1.8)         M22       Systemic lupus explore involved issue       0.4       0.0       4.2 (1.7.47, 7.5, 7.8, 1.8)         M23       Systemic lupus explore involved issue       0.4       0.0       2.2 (1.7.6, 7.8, 1.8)         M25       Systemic lupus explore involved issue       0.4       0.0       2.2 (1.7.4, 1.7, 1.5, 7.8, 1.8)         M26       Systemic lupus explore involved issue       0.4       0.2       2.3 (1.7.6, 7.8, 1.8)         M27       Systemic lupus explore involved issue       0.4       0.2       2.3 (1.1.6)         M27       Systemic lupus explore involved issue       0.4       0.2       2.3 (1.1.6)         M28       Systemic lupus explore involved issue       0.4       0.2       2.3 (1.1.6)	L20 L29	Pruritus	∠.ə 11.4	2.1	1.	+ (1.1-1.7) 2 (1.0-1.3)	- <b>-</b>		*			
Libben planus       0.1       0.0       11.5 (22-46.0)         Libben multiform       0.2       0.0       55 (22-313.4)         Libben multiform       0.2       0.0       15.7 (25-54.8)         Libben multiform       0.0       0.0       0.0       0.0         VIL Upmons, sign ad abornal clinical and baboration (Insure MCP (MOPAP))       0.0       0.0       0.0         VIL Symptoms, sign ad abornal clinical and baboration (Insure MCP (MOPAP))       0.0       0.0       0.0         R65       Systemic Inflammatory Response Syndrome       2.5       2.3       1.3 (1.1-1.6)         100       4.4       2.1       1.1 (1.1-1.6)       -         100       5.5       0.4       1.6 (1.3 (1.1-1.6)       -         100       7.6 (1.7-16.2)       -       -       -         100       0.0       5.7 (1.7-16.2)       -       -         100       0.0       7.7 (1.7-16.2)       -       -       -         100       0.0       5.7 (1.7-16.2)       -       -       -       -         100       0.0       5.7 (1.7-16.2)       -       -       -       -       -         100       1.2 (1.10.1.1.6)       -       -       -	L40-L45	Papulosquamous disorders	1.1	0.9	1.	4 (1.0-1.9)			*			
Link         Crystemic industry metabolis         U.S. (0)         Sol (2-5134)           M2L         Discusses of the metabolis state and connective tissue (MOX-M99)         Al (1.7-14.7)         Al (1.7-14.7)           M32         Systemic lupus explanel involvement of connective tissue 0.4 0.2 2 24 (1.5-5.0)         Al (1.7-14.7)         Al (1.7-14.7)           M35         Systemic lupus explanel involvement of connective tissue 0.4 0.2 2 23 (1.5-5.0)         Al (1.7-14.7)         Al (1.7-14.7)           M35         Systemic lupus explanel involvement of connective tissue 0.4 0.2 2 23 (1.5-5.0)         Al (1.7-14.7)         Al (1.7-14.7)           M35         Systemic lupus explanel involvement of connective tissue 0.4 0.2 2 23 (1.5-5.0)         HR PCR COR IC signification of the proceeding	L43	Lichen planus	0.1	0.0	11	.5 (2.9-46.0)			→ *	*	*	*
2.10       2.10	L51 L80	Erymerna muttrorme Vitiligo	0.2	0.0	5. 17	o (2.3-13.4) 7 (5 7-54 8)			*	*	*	*
M32       Systemic lugue systemic involvement of connective tissue       0.1       0.0       4.9 (17.14.7)         X VII. Symptoms, signs and abnormal clinical and aboratory findings, NEC (R00-R89)       1.3 (1.14.6)       1.4 (2.2 ± 2.6)       1.5 (2.14.7)         R65       Systemic Inflammatory Response Syndrome       2.5 ± 2.3 (1.3.1(1.14.6))       1.5 (1.14.7)       1.5 (1.14.7)         R65       Systemic Inflammatory Response Syndrome       2.5 ± 2.3 (1.3.1(1.14.6))       1.5 ± 2.5	200	X III. Diseases of the musculoskeletal system and connective ti	issue (l	M00-M9	99) ''	(0.7 04.0)			**	*	*	*
M35       Other systemic involvement of connective lissue XVII. Process of the arrows system (Advanced Links and Absord and Links and XVII. HR(85% CI) AE % AE %       HR PCR COR IC sig. sig. sig. sig. sig. sig. sig. sig.	M32	Systemic lupus erythematosus	0.1	0.0	4.	9 (1.7-14.7)			- :		:	:
Ref       Systemic Inflammatory Response Syndrome       2.5       2.3       1.3 (1,11.6)         Code       Disease categories       ICI       Non-ICI HR(95%, C)       HR       PCR COR IC         L Certain Infectious and parasitic diseases (A00-B99)       4.4       4.2       1 (2,11.1.4)       •         Disease categories       ICI       Non-ICI HR(95%, C)       HR       PCR COR IC       sig. sig. sig. sig. sig.         Disease categories       ICI       Non-ICI HR(95%, C)       HR       PCR COR IC       sig. sig. sig. sig. sig. sig. sig.         Disease categories       ICI Non-ICI HR(95%, C)       HR       PCR COR IC       sig. sig. sig. sig. sig. sig. sig. sig.         Disease categories       ICI Non-ICI HR(95%, C)       HR       PCR COR IC       sig. sig. sig. sig. sig. sig. sig. sig.	M35	Other systemic involvement of connective tissue	0.4	0.2	2.	8 (1.5-5.0)			*	*	*	*
Code       Disease categories       CI       Non-ICI HR(95% CI)       HR PCR COR IC sig. sig. sig. sig.         L Carlain infectious and parasitic diseases (A00-B99)       A1       Other sepsis       4.4       4.2       1.2(1,1-1.4)         Discrete register       1.1       1.4       4.1       1.3(1,1-1.6)       •       •         Dermstophylosi       1.1       1.4       1.3(1,1-1.6)       •       •       •         Discretes of Imerial metabolic diseases (E00-E90)       0.5       0.4       1.0(1,5.2,5)       •       •         E33       Discretes of Imerial metabolic diseases (E00-E90)       0.0       5.7       1.2(1,1-1.4)       •       •       •         E44       Cubing's syndrome       0.1       0.0       5.7       1.2(1,1-1.6)       • <t< td=""><td>R65</td><td>Systemic Inflammatory Response Syndrome</td><td>2.5</td><td>2.3</td><td>1</td><td>3 (1.1-1.6)</td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	R65	Systemic Inflammatory Response Syndrome	2.5	2.3	1	3 (1.1-1.6)						
L Cartain Infactious and parasitic diseases (A00-B99)Sig.Sig.Sig.Sig.A41Other sepsis4.44.21.2 (1.1-1.4)••2223.11.3 (1.1-1.6)••••B33Dermatophytosis2.3 (11.3 (1.1-1.6)•••B34Dermatophytosis0.05.7 (1.7-19.8)••••E11Type 2 diabetes mellius0.08.7 (1.2 (1.1-1.4)•••••E24Cushing's syndrome0.10.05.7 (1.7-19.8)••••••F05Delifrum, not induced by alcohol and other psychoactive substances3.93.21.5 (1.3-1.9)•••												
A41       Other sepsis       4.4       4.2       1.2 (1.1.4.)       •         B32       Zostie [herps zoster]       3.2       3.1       1.3 (1.1.4.)       •         B35       Dematophytosis       4.1       4.0       1.3 (1.1.4.)       •         B35       Dematophytosis (J7.3') $V.$ Endocrine, nutritional and metabolic diseases (E00-E90) $V.$ Menda and behavioural disorders (F00-99) $V.$ Microsense of the ear and metabolis disorders (F00-F99) $V.$ Diseases of the ear and metabolis process (F00-F99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the ear and mastoid process (F00-H99) $V.$ Diseases of the earand mastoid process (F00-F09)	Code	Disease categories			Non-I	CI HR(95% CI)			HR	PCR	COR	IC
Lover (neurops 20ster)         3.2         3.1         1.3(1.1-16)           B35         Dermatophytosis         0.5         0.4         1.3(1.1-16)           B45         Dermatophytosis         0.5         0.4         1.6(1.1-16)           W. Endocrino, nitritional and metabolic diseases (E00-E90)         0.5         0.4         1.6(1.0-2.6)           E11         Type 2 diabetes mellitus         0.0         5.7 (1.7-19.8)         -           E23         Cushing synchrome tabolition         4.5         3.4         1.6(1.3-1.8)           E24         Cushing not induced by alcohol and other psychoactive substances         3.9         3.2         1.5 (1.3-1.8)           F30-F39         Mod plafective) disorders (F00-99)         1.0         9         1.2 (1.1/1.0-1.3)         -           F30-F39         Mod plafective) disorders (F00-99)         3.8         3.0         1.6 (1.3-1.9)         -<	Code	Disease categories I. Certain infectious and parasitic diseases (A00-B99)		ICI AE %	Non-I AE %	CI HR(95% CI)	-		HR sig.	PCR sig.	COR sig.	IC sig.
B559       Prouncycytosic (17.3°)       0.5       0.4       1.6 (1.0.2.6)         W. Endocrine, nutritional and matabolic diseases (E00-E90)       9.0       8.7       1.2 (1.1.4.4)         E41       Type 2 diabetes mellitus       9.0       8.7       1.2 (1.1.4.4)         E42       Custing's syndrome       0.1       0.0       5.7 (1.7.19.8)         E43       Disorders of mineral metabolism       4.5       3.4       1.6 (1.3.1.9)         V. Mental and behavioural disorders (F00-59)       1.0       9       1.2       1.1 (1.0-1.3)         V. Diseases of the nervous system (G00-G99)       1.0       9       1.2       1.1 (1.0-1.3)         VI. Diseases of the eva and adnexa (H00-H59)       0.3       0.1       2.1 (1.6.5.3)	Code	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis		ICI AE %	Non-I AE %	CI HR(95% CI)	•		HR sig. *	PCR sig.	COR sig.	IC sig.
InterpretationN: Endocrine, nutritional and metabolic diseases (E60-E90)N: I $2(1,1-14)$ E21Type 2 diabetes mellitus0.05.7 (1.7-19.8)E32Disorders of mineral metabolism4.53.41.6 (1.3-1.9)F30-F30Mond [affactive] disorders (F00-99)10.911.21.1 (1.0-1.3)F30-F30Mond [affactive] disorders (F30-F39)10.912.21.5 (1.3-1.8)F30-F30Mond [affactive] disorders (F30-F39)10.911.21.1 (1.0-1.3)F30-F30Mond [affactive] disorders (F30-F39)10.911.21.1 (1.0-1.3)F30-F30Mond [affactive] disorders (F40-F39)10.911.21.7 (1.5-2.5)G40Epilepsy3.83.01.6 (1.5-2.5)-G41Herniplegia1.61.00.1 (0.7.2.3.3)-G43Other paralytic syndromes0.10.10.25.8 (1.5-23.3)G44Diseases of the ear and mastoid process (H60-H95)H2Cataract and other and mastoid process (H60-H95)H2Parachysand Lacycardia0.90.61.6 (1.1-2.4)H31Portal vein thrombosis0.10.05.8 (1.5-23.3)H31Portal vein thrombosis0.10.05.8 (1.2-3.4)H45Cardiac arrest4.42.72.0 (1.2-2.4)H51Intracerebral haemorrhage0.40.32.0 (1.2-3.3)H53Diseases o	<b>Code</b> A41 B02 B35	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatonby/tosis		ICI AE % 4.4 3.2 4 1	Non-I AE % 4.2 3.1 4.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6)	*		HR sig. * *	PCR sig.	COR ∣ sig. ∶	IC sig.
11       type 2 diagetes mellitus       9.0       8.7       7.2 (1.1-1.4)       •         224       Cushing's syndrome       0.1       0.0       5.7 (1.7-1.8)       •       •         E83       Disorders of mineral metabolism       4.5       3.4       1.6 (1.3-1.9)       •       •       •         F05       Delirium, not induced by alcohol and other psychoactive substances       3.9       3.2       1.5 (1.3-1.8)       •       •       •         F065       Delirium, not induced by alcohol and other psychoactive substances       3.9       3.2       1.5 (1.3-1.8)       • <td< td=""><td><b>Code</b> A41 B02 B35 B59</td><td>Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pheumocytosis(J17.3°)</td><td></td><td>ICI AE % 4.4 3.2 4.1 0.5</td><td>Non-I AE % 4.2 3.1 4.0 0.4</td><td>CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6)</td><td>+ + +</td><td></td><td>HR sig. * *</td><td>PCR sig.</td><td>COR sig.</td><td>IC sig.</td></td<>	<b>Code</b> A41 B02 B35 B59	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pheumocytosis(J17.3°)		ICI AE % 4.4 3.2 4.1 0.5	Non-I AE % 4.2 3.1 4.0 0.4	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6)	+ + +		HR sig. * *	PCR sig.	COR sig.	IC sig.
Lat.Durange optimiserCirl0.00.1<	<b>Code</b> A41 B02 B35 B59	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(417.3°) V. Endocrine, nutritional and metabolic diseases (E00-E90)		ICI AE % 4.4 3.2 4.1 0.5	Non-I AE % 4.2 3.1 4.0 0.4	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 4 0 (4	+ + +		HR sig. * * *	PCR sig.	COR   sig. :	IC sig.
V. Mental and behavioural disorders (F00-99)Internal of the transmission of the previous system (600-699)F05Delinium, not induced by alcohol and other psychoactive substances3.9 $3.2$ $1.5$ ( $1.3.1.8$ )F06Delinium, not induced by alcohol and other psychoactive substances $3.9$ $3.2$ $1.5$ ( $1.3.1.8$ )F06Delinium, not induced by alcohol and other psychoactive substances $3.9$ $3.2$ $1.5$ ( $1.3.1.8$ )F06Delinipsy $3.8$ $3.0$ $1.6$ ( $1.3.1.9$ ) $\bullet$ G81Hemiplegia $1.6$ $1.0$ $1.9$ ( $1.5.2.5$ ) $\bullet$ G83Other paralytic syndromes $0.1$ $0.1$ $2.7$ ( $1.3.5.3$ ) $\bullet$ F18Cataract and other disorders of lens in diseases classified elsewhere $0.1$ $0.1$ $2.4$ ( $0.96.3$ )F18Cataract and other disorders of lens in diseases classified elsewhere $0.1$ $0.0$ $5.9$ ( $1.2.29.4$ )H67Otitis media in diseases classified elsewhere $0.1$ $0.0$ $5.9$ ( $1.2.29.4$ )H67Otitis media in diseases classified disewhere $0.1$ $0.0$ $5.6$ ( $1.8.17.3$ )H7Paroxysmal tachycardia $0.9$ $0.6$ $1.6$ ( $1.4.2.4$ )H67Notal vein thrombosis $0.1$ $0.0$ $4.4$ ( $1.2.16.5$ )KDiseases of the respiratory system (M00-M39) $1.6$ $1.4$ ( $1.2.16.5$ )KN Diseases of the skin and subcutaneous tissue (L00-L99) $1.7$ ( $1.5.19$ ) $1.6$ K10Diseases of the skin and subcutaneous tissue (L00-L99) $1.6$ $0.5$	Code A41 B02 B35 B59 E11 F24	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) N. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cusbind's surdicime		ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5 7 (1.7-10.9)	* * - * *		HR sig. * * *	PCR sig.	COR ∣ sig. :	IC sig.
F05       Delinium, not induced by alcohol and other psychoactive substances       3.9       3.2       1.5 (1.3-1.8)         F03-F33       Mood [affective] (disorders[F3:07:93)       1.9       11.2       1.1 (1.0-1.3)         F03-F33       Mood [affective] (disorders[F3:07:93)       3.8       3.0       1.6 (1.3-1.9)         G81       Hemiplegia       1.6       1.0       1.9 (1.5-2.5)         G83       Other paralytic syndromes       0.3       0.1       2.7 (1.3-5.3)         WI. Diseases of the eye and adnexa (H00-H59)       0.1       0.0       5.9 (1.2-29.4)         H28       Cataract and other disorders of lens in diseases classified elsewhere       0.1       0.1       0.4 (1.2-2.3)         H27       Paroxysenal tachycardia       0.9       0.6 (1.6 (1.1-2.4))	Code A41 B02 B35 B59 E11 E24 E83	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pheumocystosis(J17.3*) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabets mellitus Cushing's syndrome Disorders of mineral metabolism		ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9)	*		HR sig. * * * *	PCR sig.	COR I sig. :	IC sig.
row-rssmodul (antecurre) disorders (r-sur-rss)interve (rss) (r-sur-rss)interve (rss) (r-sur-rss)G40Epilepsy3.83.01.6 (1.3.1.9)G41Hemiplegia1.61.01.9 (1.5.2.5)G43Other paralytic syndromes0.30.12.7 (1.3.5.3)WI. Diseases of the eye and adnexa (H00-H59)0.10.12.4 (0.9.6.3)H43Cataract and other disorders of lens in diseases classified elsewhere0.10.12.4 (0.9.6.3)H45Cataract and other disorders of lens in diseases classified elsewhere0.10.15.9 (1.2.29.4)H46Cardiac arrest4.42.72.0 (1.7.2.3)H47Paroxysmal tachycardia0.90.61.6 (1.1.2.4)H61Intracerebral haemorrhage0.40.32.0 (1.2.3.3)H45Status asthmaticus0.10.05.6 (1.8.1.7.3)H46Status asthmaticus1.61.41.3 (1.0.1.7)H57Hypersensitivity pneumonitis due to organic dust0.10.05.7 (1.8-19.7)J67Hypersensitivity pneumonitis due to organic dust0.10.05.7 (1.8-19.7)J67Hypersensitivity pneumonitis due to and nusbcutaneous tissue (L00-L99)1.10.55.2 (1.5.3.1)J74Ecorine sweat disorders0.30.52.2 (1.5.3.1)J74Ecorine sweat disorders0.50.52.2 (1.5.3.1)J74Ecorine sweat disorders0.50.52.2 (1.5.3.1)J74Ecorine sweat disorders0.	<b>Code</b> A41 B02 B35 B59 E11 E24 E83	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3*) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mentai and behavioural disorders (F00-99)		ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.8)	*		HR sig. * * * * *	PCR sig.	COR i sig. :	IC sig.
G40Epilepsy (38)3.83.01.6 (1.3.1.9) (1.9 (1.5.2.5)G81Hemiplegia1.61.01.9 (1.5.2.5)G83Other paralytic syndromes0.30.12.7 (1.3.5.3)WI. Diseases of the eya and adnexa (H00-H59)0.10.15.8 (1.5.23.3)H20Charact and other an anstoid process (H60-H95)0.10.05.8 (1.5.23.3)H67Ottis media in diseases classified elsewhere0.10.05.9 (1.2.29.4)H67Ottis media in diseases of the circulatory system (100-199)0.10.05.9 (1.2.29.4)H67Paroxysmal tachycardia0.90.61.6 (1.1.2.4)H61Intracerbral haemorthage0.40.32.0 (1.2.3.3)H61Intracerbral haemorthage0.40.32.0 (1.2.3.3)H7Paroxysmal tachycardia0.10.05.6 (1.8-17.3)K. Diseases of the respiratory system (100-J99)1.61.4 (1.2.16.5)J46Status astimaticus0.10.04.4 (1.2.16.5)K. Diseases of the skin and subcutaneous tissue (L00-L99)1.10.02.4 (1.1.5.1)K.M. Diseases of the skin and subcutaneous tissue (L00-L99)1.10.02.2 (1.5.3.1)M40Disorders of continuity of bone0.90.51.9 (1.3.2.8)M41Disorders of continuity of bone0.90.51.9 (1.3.2.8)M44Disorders of continuity of bone0.90.51.2 (1.5.1.9)K.M. Diseases of the skin and abnormal clinical and laboratory findings, KPC (R00-R99	<b>Code</b> A41 B02 B35 B59 E11 E24 E83 F05 E30 F05	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) V. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance disord (officient disorders (20.5°)	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.0	1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.9) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8)	* * *		HR sig.	PCR sig.	COR   sig. :	IC sig.
G81       Hemiplegia       1.6       1.0       1.9 (1.5.2.5)	A41 B02 B35 B59 E11 E24 E83 F05 F30-F39	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Presumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes meliitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by a toholn and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (600-690)	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2	1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3)	* * * *_		HR sig.	PCR sig.	COR I sig. :	IC sig.
GB3       Other paralytic syndromes       0.3       0.1       2.7 (1.3.5.3)         WI. Diseases of the eye and admxa (H00-H59)       0.1       0.0       5.8 (1.5.2.3.)         H28       Cataract and other disorders of lens in diseases classified elsewhere       0.1       0.1       0.4 (0.9.6.3.)         WI. Diseases of the ear and mastoid process (H60-H95)       0.1       0.1       0.4 (0.9.6.3.)         WI. Diseases of the circulatory system (00-H99)       0.1       0.1       0.4 (0.9.6.3.)         K. Diseases of the circulatory system (00-H99)       0.4       0.5       5.9 (1.2.29.4)         H47       Paroxysmal tachycardia       0.9       0.6       1.6 (1.1.2.4.)         H61       Intracerebral haemorrhage       0.4       0.3       5.0 (1.2.2.3.)         H45       Cataract and bas outpoutsoid       0.1       0.0       5.6 (1.8.17.3.)         K. Diseases of the respiratory system (J00-J99)       0.1       0.0       5.6 (1.8.17.3.)         K. Diseases of the digestive system (K00-K93)       0.1       0.1       2.4 (1.1.5.1)         K. Diseases of the skin and subcutaneous tissue (L00-L99)       1.0 (1.5.7.1(1.5.1.9)       4.4 (1.2.16.5)         K. Diseases of the musculostaletal system and connective tissue (M00-M99)       1.9 (1.5.3.1)          K. M. Diseases	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocytosis(J17.3*) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(750-F39) V. Diseases of the nervous system (G00-G99) Epilepsy	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.2 (1.1-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9)	* * * * * *		HR sig.	PCR sig.	COR   sig. :	IC sig. *
vir. Juscasses of the eye and adrexa (H00-H59)H28Cataract and other disorders of lines in diseases classified elsewhere0.10.05.8 (1.5-23.3)H30Chorioretinal inflammation0.10.10.12.4 (0.9-6.3)WII. Diseases of the ear and mastoid process (H60-H95)Image: Colored colore	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81	Disease categories I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) V. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, notinduced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0	1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9)	* * * * *	<b>•</b>	HR sig. • • • •	PCR sig.	COR   sig. :	IC sig.
Inc.Only of the use of the air indecases dassingle disconteriorO.1O.0O.1O.0O.1<	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G83	Disease categories I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3*) W. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism U. Mental and behavioural disorders (F00-99) Delirium, not induced by a lochol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes	Des s	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1	1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3)	* * * * *	<b>-</b>	HR sig.	PCR :	COR   sig.	IC sig. *
VIII. Diseases of the ear and mastoid process (H60-H95)Intervention of the constraint of the c	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 H28	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocytosis(J17.3*) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) VI. Diseases of the nervous system (G00-G99) Eleiplepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ye and adnexa (H00-H59) Centarget and other given of them is indices of lengender	2005	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.2 (1.1-1.4) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 6.8 (4.6.72.32)	* * * * *		HR sig. • • • • • • • • • • • • • •	PCR :	COR   sig.	IC sig. *
H67Otitis media in diseases classified elsewhere0.10.0 $5.9 (1.2-29.4)$ <i>IK</i> Diseases of the circulatory system (100-J99)	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G83 H28 H30	Disease categories I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders (700-F39) Epilepsy Hemiplegia Other paralytic syndromes VI. Diseases of the open and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretina inflammation	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-4.3) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.6 (1.3-1.9) 1.6 (1.3-1.9) 1.5 (1.5-2.3) 5.8 (1.5-2.3.3) 5.4 (1.5-2.3.3)	* * * * -	<b>-</b>	HR sig.	PCR	COR   sig. :	IC sig. *
IX. Diseases of the circulatory system (100-199)         Ide Cardiac arrest       4.4       2.7       2.0 (1.7-2.3)         Ide Cardiac arrest       0.9       0.6       1.6 (1.1-2.4)         Ide Cardiac arrest       0.4       0.3       2.0 (1.2-3.3)         Ide Cardiac arrest       0.4       0.3       2.0 (1.2-3.3)         Ide Cardiac arrest       0.1       0.0       5.6 (1.8-17.3)         X. Diseases of the respiratory system (J00-J99)       -       -         J46       Status asthmaticus       1.6       1.4       1.3 (1.0-1.7)         J47       Hypersensitivity pneumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         X. Diseases of the skin and subcutaneous tissue (L00-L99)       -       -       -         X. Diseases of the skin and subcutaneous tissue (L00-L99)       -       -       -         X. M. Diseases of the skin and subcutaneous tissue (L00-L99)       -       -       -         M80       Oscorporasis with pathological fracture       0.7       0.5       1.9 (1.8-2.8)       -         M80       Disorders of continuity of bone       0.9       0.5       2.2 (1.5-3.1)       -       -         X. Will Symptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)       -	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G83 H28 H30	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delinium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the equival and and ther disorders (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the equival and there syndromes VIII. Diseases of the equival and there and mastoid process (H60-H95)	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.1	1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3) 2.4 (0.9-6.3)	* * * * *		HR • • • • • • • • • • • • • • • • • • •	PCR sig.	COR   sig.	IC sig. *
HT       Parton books       4.4       2.7       2.011.72.31       •       •       •         HT       Parton books       0.6       1.6 (1.1.2.4)       •	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 G81 H28 H30 H28 H30 H67	Disease categories  I. Certain Infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Preumocystosis(J17.3°) V. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of nineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleiplepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewhe Chorioretinal inflammation VII. Diseases (tabel casalified elsewhere)	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.1 0.0 0.1 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 5.9 (1.2-29.4)	* * * * -		HR sig. • • • • • • • • • • • • • • • • • • •	PCR :	COR   sig.	IC sig. *
i61       Intracerebral hadmornage       0.4       0.3       2.0 (1/2.3.3)         i81       Portal vein thrombosis       0.1       0.0       5.6 (1.8-17.3)         X. Diseases of the respiratory system (J00-J99)            J46       Status astimaticus       1.6       1.4       1.3 (1.0-1.7)         J67       Hypersensitivity preumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         J67       Hypersensitivity preumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         J7       LDiseases of the digestive system (K00-K93)            J81       Discases of the skin and subcutaneous tissue (L00-L99)            L74       Ecorine sweat disorders       0.1       0.0       5.7 (1.6-19.7)          L89       Decubius uicer and pressure area       8.8       6.2       1.7 (1.5-1.9)           W00       Osteoporosis with pathological fracture       0.7       0.5       1.9 (1.3-2.8)           M04       Disorders of continuity of bone       0.9       0.5       2.2 (1.5-3.1)            X/ Mi/ Symptoms, signs and a	Code A41 B02 B35 B59 E11 E24 E33 F05 F30-F39 G40 G81 G83 H28 H30 H67	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretina inflammatio VIII. Diseases of the eye and matoid process (H60-H95) Ottis media indiseases classified elsewhere IV. Diseases of the circulatory system (I00-I99) Cataract	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.1 0.0 2.7	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 5.9 (1.2-29.4) 2.0 (4.7.2.3)	* * * * *		HR sig. • • • • • • • • • • • • • • • • • • •	PCR :	COR I	IC sig.
181       Portal vein thrombosis       0.1       0.0       5.6 (1.8-17.3)         X. Diseases of the respiratory system (J00-J99)       1.6       1.4       1.3 (1.0-1.7)         J46       Status asthmaticus       1.6       1.4       1.3 (1.0-1.7)         J67       Hypersensitivity pneumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         X.I. Diseases of the digestive system (X00-X93)       -       -       -         X.M. Diseases of the skin and subcutaneous tissue (L00-L99)       0.1       0.0       2.4 (1.1-5.1)         X.I. Diseases of the skin and subcutaneous tissue (L00-L99)       -       -       -         M2.0       Discorders of continuity of bone       0.1       0.0       5.1 (1.6.1-2.8)       -       -         M84       Disorders of continuity of bone       0.9       0.5       1.7 (1.1-2.5)       -       -       -         X.W. Isymptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)       -       -       -       -       -         X.W. Isymptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)       -       -       -       -         X.W. Isymptoms, signs and abnormal clinical and laboratory findings, NEC (R00-R99)       -       -       -       -         X.V. Isym	Code A41 B02 B35 B59 E11 E24 E24 F30-F39 G40 G81 G83 H28 H30 H67 H67 H46	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substanc Mood [affective] disorders(F00-99) Delirium, not induced by alcohol and other psychoactive substanc Mood [affective] disorders(F00-99) Delirium, not induced by alcohol and other psychoactive substanc Mood [affective] disorders(F00-F99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ere and dnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VII. Diseases of the ere and anastoid process (H60-H95) Ottils media in diseases classified elsewhere K. Diseases of the circulatory system (I00-I99) Cardiac arrest Paroxysmal tachycardia	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 0.1 4.4 0.9	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.0 0.1 0.0 2.7 0.6	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-23.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4)	* * * * -		HR sig. • • • • • • • • • • • • • • • • • • •	PCR :	COR   sig. :	IC sig.
A. Diseases of the reginatory system (volves)         J66       Status asitimaticus       1.6       1.4       1.3 (1.0-1.7)         J67       Hypersensitivity pneumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         X1       Diseases of the digestive system (X00-K93)       0.2       0.1       2.4 (1.1-5.1)         X8       Acute appendicitis       0.2       0.1       2.4 (1.1-5.1)         X8       Diseases of the skin and subcutaneous tissue (L00-L99)       0.1       0.0       5.7 (1.6-19.7)         L89       Decubius ulear and pressure area       8.8       6.2       1.7 (1.5-1.9)       •       •         M80       Osteoporosis with pathological fracture       0.7       0.5       1.9 (1.3-2.8)       •       •       •         M84       Discoders of continuity of borne       0.9       0.5       2.2 (1.5-3.1)       •       •       •       •         X Will Symptoms, signs and abormal clinical and laboratory findings, NEC (R00-R99)       •	Code A41 B02 B35 S59 E11 E24 E83 F30-F39 G81 G81 G83 H28 H30 H67 H67 I46 I47 I61	Disease categories  I. Certain Infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dematophytosis Preumocystosis(J17.3°) V. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the eye and adnexa (H00-H59) Catract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the eer and mastoid process (H60-H95) Ottis media in diseases classified elsewhere IX. Diseases of the icruitatory system (100-I99) Cardiac arrest Paroxysmal tachycardia Intracerbaral haemorthage	ces nere	ICI AE % 4.4 3.2 4.5 9.0 0.1 0.5 9.0 0.1 0.3 0.1 0.1 0.1 4.4 0.9 0.4	Non-J AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.0 0.1 0.0 0.2 7 0.6 0.3	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4)	* * * * * *		HR sig.	PCR :	COR	IC sig.
1.67       Hypersensitivity pneumonitis due to organic dust       0.1       0.0       4.4 (1.2-16.5)         XI. Diseases of the digestive system (K00-K93)       0.2       0.1       2.4 (1.1-5.1)         XI. Diseases of the skin and subcutaneous tissue (L00-L99)       0.1       0.0       5.7 (1.6-19.7)         L74       Ecorine sweat disorders       0.1       0.0       5.7 (1.6-19.7)         L89       Decubitus ulcer and pressure area       8.8       6.2       1.7 (1.5-1.9)         XII. Diseases of the musculoskeletal system and connective tissue(M00-M99)       •       •       •         M60       Osteoporosis with pathological fracture       0.9       0.5       2.2 (1.5-3.1)       •         XII. Symptoms, signs and abnormal clinical and laboratory findings, IECC (R00-R99)       •       •       •       •         R56       Convulsions       1.9       1.6       1.5 (1.1-1.9)       •       •       •         XII. Injury, poisoning and certain other consequences of external causes (S00-T98)       1.6       1.0 (1.5-2.6)       •       •       •         S32       Fracture of founder and upper arm       0.4 (2.2 2.6 (1.5-4.6)       •       •       •       •         S42       Fracture of femur       0.7       0.4 (2.2 2.0 (1.0-3.8)       •	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 H28 H30 H67 I46 I47 I61 I81	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(750-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretina indiseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Ottis media indiseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorders of lens in diseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorders of lens in diseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorders of lens in diseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorders of lens in diseases classified elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorder disorders disease elsewhere M. Diseases of the exand mastoid process (H60-H95) Cataract and the disorder disorde	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 4.5 0.1 4.5 0.3 0.1 4.4 0.9 0.1 4.4 0.9 0.4 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.0 0.1 0.0 0.1 0.0 0.2 7 0.6 0.3 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 3.6 (1.8-17.3)	* * * * * *		HR sig.	PCR :	COR   sig. :	IC sig. * *
X I Diseases of the digestive system (K00-K93)       0.2       0.1       2.4 (1.1-5.1)         K35       Acute appendictis       0.2       0.1       2.4 (1.1-5.1)         X II. Diseases of the skin and subcutaneous tissue (L00-L99)       0.1       0.0       0.1	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G83 H28 H30 H67 H47 I61 I47 I61 J46	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, notinduced by alcohol and other psychoactive substanc Mood [affective] disorders(F30-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ear and matci process (H60-H95) Ottis media in disorders of lens in diseases classified elsewh Chorioretina inflammation VII. Diseases of the ear and matci process (H60-H95) Ottis media in diseases classified elsewhare IX. Diseases of the ear and matci process (H60-H95) Ottis media in diseases classified elsewhare Paroxysmal tachycardia Intracerbral haemorrhage Portal vein trombosis X. Diseases of the respiratory system (J00-J99) Status asthmaticus	ces nere	ICI % 4.4 4.4 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 0.3 0.1 0.1 0.1 4.4 0.9 0.4 0.1 1.6	Non-J AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.1 0.0 0.1 0.0 2.7 0.6 0.3 0.0 1.4	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.2-3.3) 1.6 (1.1-2.4) 2.0 (1.2-3.5) 1.6 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.2-3.5) 1.7 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.2-3.5) 1.7 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.1-2.4) 2.0 (1.2-3.5) 1.7 (1.2-3.5) 1.	* * * * * *		HR sig.	PCR :	COR	IC sig.
K35       Acute appendicitis       0.2       0.1       2.4 (1.1-5.1)         X II. Diseases of the skin and subcutaneous tissue (L00-L99)       0.1       0.0       5.7 (1.6-19.7)         L74       Ecorine sweat disorders       0.1       0.0       5.7 (1.6-19.7)         Decublius ulcer and pressure area       8.8       6.2       1.7 (1.5-1.9)         M80       Osteoporosis with pathological fracture       0.7       0.5       1.9 (1.3-2.8)         M84       Disorders of continuity of bore       0.9       0.5       2.2 (1.5-3.1)         X WII. Symptoms, signs and abormal clinical and laboratory findings, NEC (R00-R99)       1.9 (1.6       1.5 (1.1-1.9)         X WII. Symptoms, signs and abormal clinical and laboratory findings, NEC (R00-R99)           Status of the musculoskeletal system and consective tissue (N00-M99)           Status of the musculoskeletal system and consective tissue (N00-M99)           KUII. Symptoms, signs and abormal clinical and laboratory findings, NEC (R00-R99)           X WII. Symptoms, signs and abormal clinical and laboratory findings, NEC (R00-R99)           X Kuit the symptom actions       1.9       1.6       1.5 (1.1-1.9)         X K. Injury, poisoining and certain other consequences of e	Code A41 B02 B35 S59 E11 E24 E83 F30-F39 G81 G83 H28 H30 H67 H67 H67 H61 H81 J46 J67	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Preumocytosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleiplepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewhe Chorioretinal inflammation VIII. Diseases of the ever and mastoid process (H60-H95) Ottis media in diseases classified elsewhere IX. Diseases of the recrulatory system (I00-I99) Cardica arest Paroxysmal tachycardia Intracerbara haemorhage Portal vein thrombosis X. Diseases of the respiratory system (J00-J99) Status asthmaticus Hypersensitivity pneumonitis due to organic dust	ces	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 0.1 4.4 0.9 0.4 0.1 1.6 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.0 0.1 0.0 0.1 0.0 0.2 0.7 0.6 0.3 0.0 1.4 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 5.6 (1.8-17.3) 3.5 (1.8-17.3) 1.3 (1.0-1.7) 1.3 (1.0-1.7) 3.4 (1.2-16.5)	* * * * * * * * * * * * * * * * * * *		HR sig.	PCR :	COR   sig. :	IC sig.
X.R. Useases of the skin and subcutaneous tissue (L00-L99)         174       Excine sweat disorders         0.1       0.0       5.7 (1.6-19.7)         1.89       Descubitus ulcar and pressure area       8.8       6.2       1.7 (1.5-1.9)         X.R. Diseases of the musculoskeletal system and connective tissue (M00-M99)       • • • • • • • • • • • • • • • • • • •	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 H30 H67 H67 H67 H61 I81 J46 J67	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) VI. Diseases of the nervous system (G00-G99) Eellipups Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the examt matoid process (H60-H95) Othis media in diseases classified elsewhere IX. Diseases of the recrulatory system (I00-199) Cardiac arest Paroxysmal tachycardia Intraorebral hemorrhage Portal vein thrombosis X. Diseases of the respiratory system (J00-J99) Status astimaticus Hypersensitivity pneumonitis due to organic dust X. J. Diseases of the eigentive system (K00-K93)	ces nere	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 1.6 0.1 4.4 9.0 0.1 1.6 0.1 1.6 0.1 1.6 0.1	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 11.2 3.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 1.4 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-23.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 5.6 (1.8-17.3) 1.3 (1.0-1.7) 4.4 (1.2-16.5)	* * * * * * * *		HR sig.	PCR :	COR   sig. :	IC sig.
Low moder values         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.0         0.1         0.0         0.1         0.0         0.0         0.0         0.1         0.0         0.0         0.0         0.1         0.0         0.0         0.1         0.0         0.1         0.0         0.0         0.1         0.0         0.1         0.0         0.0         0.0         0.1         0.0         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.1         0.0         0.0         0.1         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0         0.0	Code A41 B02 B35 B59 E11 E24 E48 F30-F39 G40 G81 G83 H28 H30 H67 H47 H61 B1 J46 J67 K35	Disease categories  I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Custhing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, notinduced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ear and mastoid process (H60-H95) Ottis media in diseases classified elsewhere Chorioretina inflammation VII. Diseases of the ear and mastoid process (H60-H95) Ottis media in diseases classified elsewhere Ex Diseases of the erepiratory system (I00-J99) Cardiac arrest Paroxysmal tachycardia Intracerbral haemorthage Portal vein trombosis X. Diseases of the expiratory system (J00-J99) Status asthmaticus Hypersensitivity pneumonitis due to organic dust X.1 Diseases of the disesting system (K00-K93) Acute appendicitis	ses	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 9.0 0.1 0.1 0.1 0.1 0.1 0.4 0.4 0.4 0.1 0.4 0.1 0.4 0.1 0.4 0.2	Non-1 AE % 4.2 3.1 4.0 0.4 8.7 0.0 1.2 3.4 3.2 11.2 3.0 0.1 0.0 0.1 0.0 2.7 0.6 0.3 0.0 1.4 0.0 0.1	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-4.6) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.6) 2.7 (1.3-5.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.2-3.3) 5.6 (1.8-17.3) 1.3 (1.0-1.7) 4.4 (1.2-16.5) 2.4 (1.1-5.1)	* * * * * * *		HR sig.	PCR :	COR   sig. :	IC sig.
Status         Status<	Code A41 B02 B35 S59 E11 E24 E83 F30-F39 G80 G83 H28 H30 H67 H67 H67 H67 H67 H61 J61 J61 K35 L74	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Preumocytosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewhare VII. Diseases of the ervourd system (100-H99) Cardica arrest Paroxysmal tachycardia Intracerbara heamorhage Portal vein thromotis due to organic dust X. Diseases of the regiratory system (J00-J99) Status asthmaticus Hypersensitivity pneumonits due to organic dust X. J. Diseases of the skin and subcutaneous tissue (L00-L99) Fouries quest discorders X. ID Seases of the skin and subcutaneous tissue (L00-L99)	sees	ICI AE % 4.4 3.2 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 4.4 0.0 1.6 0.1 0.1 0.2 0.1	Non-I AE % 4.2 3.1 0.0 3.4 3.2 11.2 3.0 0.1 0.0 0.1 0.0 2.7 0.6 0.3 0.0 1.4 0.0 0.1 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.7 (1.1-2.4) 2.0 (1.7-2.3) 1.8 (1.1-2.4) 2.0 (1.7-2.3) 1.9 (1.1-2.4) 2.0 (1.7-2.3) 1.9 (1.1-2.4) 2.0 (1.7-2.3) 1.9 (1.1-2.4) 2.0 (1.7-2.3) 3.6 (1.1-2.4) 3.6 (1.1-2.4) 3.7 (1.1-2.4) 3.7 (1.1-2.4) 3.8 (		- - - -	HR sig.	PCR :	COR   sig. :	IC sig.
M80         Osteoporosis with pathological fracture         0.7         0.5         1.9 (1.3-2.8)          •	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 G81 H28 H30 H67 H46 H47 H61 H81 J46 J67 K35 L74 L89	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(700-69) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(700-79) U. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation UII. Diseases of the eye and matoid process (H60-H95) Ottis media in diseases classified elsewhere IX. Diseases of the erault matoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewhere IX. Diseases of the erault matoid process (H60-H95) Status astimaticus Hypersensitivity pneumonitis due to organic dust XI. Diseases of the respiratory system (I00-J99) Status astimaticus Hypersensitivity pneumonitis due to organic dust XI. Diseases of the appendicitis XI. Diseases XI	ces	ICI AE % 4.4 3.2 4.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.1 0.1 4.4 0.9 0.1 4.4 0.1 0.1 4.4 0.1 0.1 1.6 0.1 0.1 0.1 0.1 0.1 4.4 0.5 9.0 0.0 1.0 9.0 1.0 9.0 0.1 0.1 1.6 0.0 1.0 9.0 0.1 0.1 1.6 0.0 1.0 9.0 1.0 9.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1	Non-J AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-23.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.3 (1.0-1.7) 4.4 (1.2-16.5) 2.4 (1.1-5.1) 5.7 (1.6-19.7) 1.7 (1.6-19.7)	* * * * * * * * * * * * * * * * * * *		HR sig.	PCR :	COR   sig. :	IC
MM4         Disorders of continuity of bone         0.9         0.5         2.2 (1.5.3.1)          *	Code A41 B02 B35 B59 E11 E24 E33 F05 F30-F39 G40 G81 G83 H28 H30 H67 H47 H61 B1 J46 J47 K35 L74 L89	Disease categories  I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Custhing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(700-F99) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ear and mastoid process (H60-H95) Ottits media inflammation VII. Diseases of the ear and mastoid process (H60-H95) Ottits media inflammation VII. Diseases of the eigen (I00-J99) Cardiac arrest Paroxysmal tachycardia Intracerbral haemorhage Portal vein thrombosis X. Diseases of the respiratory system (J00-J99) Status asthmaticus Hypersensitivity pneumonitis due to organic dust X. I. Diseases of the skin and subcutaneous tissue (L00-L99) Acute appendicitis X. II. Diseases of the skin and subcutaneous tissue (L00-L99) Exclase are till sorders X. Diseases of the skin and subcutaneous tissue (L00-L99) Cardiac appendicitis X. II. Diseases of the pressure area X. III. Diseases of the skin and subcutaneous tissue (L00-L99)	ces nere	ICI AE % 4.4 3.2 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 4.4 0.9 0.1 0.1 1.6 0.1 0.1 0.2 0.4 0.1 0.1 0.2 0.4 0.1 0.1 0.2 0.4 0.4 0.4 0.5 9.0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0	Non-J AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.3 0.0 0.4 90	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-4.6) 1.6 (1.0-2.6) 1.2 (1.1-4.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.6) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.2-3.3) 5.6 (1.8-17.3) 1.3 (1.0-1.7) 4.4 (1.2-16.5) 2.4 (1.1-5.1) 5.7 (1.6-19.7) 1.7 (1.5-1.9)			HR sig.	PCR :	COR   sig. :	IC sig.
A rain symptons, says and above of the united and inducted y influings, REC [R00-R39]         A rain symptons, says and above of the united and inducted y influings, REC [R00-R39]         R56       Convulsions         X K, hjury, poisoning and certain other consequences of external causes (S00-T89)         S32       Fracture of houlder and upper arm         0,6       1.0         2,7       Fracture of houlder and upper arm         0,7       0,4         2,2 (1,4-3,4)         9       0,7         9,2 (2,0(1,5-2,6))	Code A41 B02 B35 B59 E11 E24 E83 F30-F39 G40 G83 H28 H30 H67 H67 H67 H61 H81 J46 J47 K35 L74 L89 M80 H80 H80 H80 H80 H80 H80 H80 H	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dematophytosis Pneumocystosis(J17.3°) W. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Custing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VII. Diseases of the ervoutary system (100-H95) Ottils media in diseases classified elsewhere IX. Diseases of the respiratory system (100-H99) Cardiac arrest Paroxysmal tachycardia Intracerbara haemorrhage Portal vein thrombosis X. Diseases of the respiratory system (K00-K33) Acute appendicitis X.II. Diseases of the skin and subcutaneous tissue (L00-L99) Eccrine sweat disorders Decublitus ulcer and pressure area X. Min. Diseases of the musculoskelatal system and connective tis Osteopronse with pathological fracture	ces nere	ICI AE % 4.4 3.2 4.5 9.0 0.1 4.5 3.9 10.9 3.8 1.6 0.3 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	Non-J AE % 4.2 3.1 4.0 0.4 3.4 3.2 11.2 3.0 0.1 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 5.0 (1.7-2.3) 5.6 (1.8-17.3) 1.3 (1.0-1.7) 4.4 (1.2-16.5) 2.4 (1.1-5.1) 5.7 (1.6-19.7) 1.7 (1.5-1.9) 1.9 (1.3-2.8) 2.9 (1.3-2.8)			HR sig.	PCR :	COR   sig. :	۲۲ ۱۹۹۹ ۱۹۹۹ ۱۹۹۹ ۱۹۹۹ ۱۹۹۹ ۱۹۹۹ ۱۹۹۹
R56         Convulsions         1.9         1.6         1.5         1.1.1.9           X /K. /njury, poisoning and certain other consequences of external causes (S00-T98)         Image: S00-T98         Image	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 G81 G81 G81 G81 G81 G81 G81	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(500-G99) Elirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(500-F39) VI. Diseases of the nervous system (G00-G99) Elirium, not induced by alcohol and other psychoactive substance Mood [affective] disorders(500-F39) VI. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VII. Diseases of the eye and matoid process (H60-H95) Citiis media in diseases classified elsewhere N. Diseases of the eirculatory system (I00-I99) Cardiac arrest Paroxysmal tachycardia Intracerberal heamorntage Portal vein thrombosis X. Diseases of the remunonitis due to organic dust X. J. Diseases of the musculoskeletal system (L00-L99) Eccrine sweat disorders Expressive system (K00-K93) Acute appendicitis X. II. Diseases of the musculoskeletal system and connective tis Osteoporosis with pathological fracture Disorders of continuity of bone	ces nere ssue (M	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 3.9 9.0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 3.4 3.2 11.2 3.0 1.1.2 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.0	Cl HR(95% Cl) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 1.5 (1.1-3.1) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.8 (1.5-23.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.2 (1.5-1.1) 3.7 (1.5-2.8) 2.2 (1.5-3.1)			HR sig.	PCR :	COR   sig. :	IC sig.
X K. Injury, poisoning and certain other consequences of external causes (500-T99)	Code A41 B02 B35 B59 E11 E24 E83 F05 F30-F39 G40 G81 G83 H30 H67 H47 H61 H47 H61 H47 H61 K35 L74 L89 M80 M84 R40	Disease categories  I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3') IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(750-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the evand adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the evand adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the evand adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the evand adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the evand adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the evand massified elsewhere X. Diseases of the respiratory system (J00-J99) Catala arrest Paroxysmal tachycardia Intracerberal haemorrhage Portal vein thrombosis X. Diseases of the interprise tystem (K00-K33) Acute appendicits X. I. Diseases of the disorders Decubitus ulcer and pressure area X. III. Diseases of the mesouloskeletal system and connective tis Osteoporosis with pathological fracture Disorders of continuity of bone X. VIII. Symptoms, signs and abnormal clinical and laboratory fin Somolence, super Alice.	ces nere ssue (M	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 9.0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0	Non-I AE % 4.2 3.1 4.0 0.4 8.7 0.0 1.0 0.4 3.2 11.2 3.0 0.1 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.3 0.0 0.3 0.0 0.3 0.0 0.0 0.0 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.0-2.6) 1.2 (1.1-4.4) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.7 (1.5-1.9) 1.7 (1.5-1.9) 1.9 (1.3-2.8) 2.2 (1.5-3.1) 29 1.7 (1.1-2.5)			HR sig.	PCR :	COR   sig. :	IC sig.
532         Fracture of number spine and pelvis         1.6         1.0         2.0 (1.5-2.6)          •	Code A41 B02 B35 B59 E11 E24 E83 F30-F39 G40 G83 H28 H30 H67 H67 H67 H67 H67 H67 K35 L74 L89 M80 M80 M80 R40 C75 R56 R56 R56 R56 R56 R56 R56 R5	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Coster [herpes zoster] Dematophytosis Preumocystosis(J17.3°) W. Diseases of mineral metabolic diseases (E00-E90) Type 2 diabetes mellitus Custing is syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(730-F39) V. Diseases of the nervous system (G00-G99) Eleineps Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewhere VII. Diseases of the revultatory system (I00-I99) Catrales arest Paroxysmal tachycardia Intracerbara heamorhage Portal vein thrombosis X. Diseases of the respiratory system (J00-J99) Status asthmaticus Hypersensitivity pneumonitis due to organic dust X. J. Diseases of the skin and subcutaneous tissue (L00-L99) Ecorine sweat disorders X. Diseases of the musculosdelat system and connective tis Discopress with pathological fracture Disorders of and anona clinical and laboratory fin Somnolence, stupor and come	ces nere ssue (M ndings,	ICI AE % 4.4 4.1 0.5 9.0 0.1 0.5 9.0 0.1 0.1 1.6 0.1 1.6 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.7 0.9 0.7 0.9 0.7 0.9 0.7 0.9 0.1 1.9 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	Non-I AE % 4.2 3.1 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.2 7 0.6 3.2 7 0.0 4 0.0 1.0 0.0 1.0 0.0 1.0 0.0 1.0 0.0 1.0 0.0 0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.5 (1.0-2.6) 1.4 (1.0-2.6) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-2.3.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 5.9 (1.2-2.9.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 5.5 (1.16-17.7) 1.7 (1.5-1.9) 1.9 (1.3-2.8) 2.9 1.7 (1.1-2.5) 2.7 (1.1			HR sig.	PCR 1	COR   sig. :	IC sig.
Great         0.4         0.2         2.0 (1.3*4.0)           S72         Fracture of femur         0.7         0.4         2.2 (1.4-3.4)           S82         Fracture of lower led, including ankle         0.3         0.2         2.0 (1.0-3.8)	Code A41 B02 B35 S59 E11 E24 E83 F05 F30-F39 G40 G81 G81 G81 G81 G81 G81 G81 G81 G81 G81	Disease categories  I. Certain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3°) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(500-G99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(500-F99) V. Diseases of the nervous system (G00-G99) Eeliplepsy Hemiplegia Other paralytic syndromes VII. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the eye and matoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the eye and matoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewhere X. Diseases of the eirculatory system (I00-I99) Cataract and other disorders (I00-H99) Cataract and the diseases classified elsewhere X. Diseases of the reprivatory system (I00-J99) Status asthmaticus Hypersensitivity pneumonitis due to organic dust X. I. Diseases of the musculoskeletal system and connective tis Osteoporosis with pathological fracture Disorders of continuity of bone X. VIII. Synapsed and abnormal clinical and laboratory fin Somnolence, stupor and coma Convulsions	ces nere ssue (M ndings, nal cau	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 9.0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0	Non-1 AE % 4.2 3.1 0.4 8.7 0.0 3.4 3.2 11.2 3.0 0.1 0.0 1.0 0.1 0.0 0.0	Cl HR(95% Cl) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.4 (1.1-2.6) 1.2 (1.1-1.4) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 2.4 (0.9-6.3) 5.8 (1.5-23.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.4 (1.1-5.1) 5.7 (1.6-19.7) 1.7 (1.5-1.9) 1.9 (1.3-2.8) 2.2 (1.5-3.1) 9 1.5 (1.1-2.5) 1.5 (1.1-1.9) 1.5 (1.1-2.5) 1.5 (1.1-2.5)			HR sig.	PCR :	COR   sig. :	IC sig.
SR2 Fracture of lower lea, including ankle 0.3 0.2 2.0 (10-3.8) - *	Code A41 B02 B35 B59 E11 E24 E33 F05 F30-F39 G40 G81 G83 H28 H30 H67 H46 H47 H61 B1 J46 J47 K35 L74 L89 M84 R40 R56 S32 S42	Disease categories  I. Cartain infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocystosis(J17.3') IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Cushing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Delirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(750-F39) VI. Diseases of the nervous system (G00-G99) Epilepsy Hemiplegia Other paralytic syndromes VII. Diseases of the ear and mastoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the ear and mastoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the ear and mastoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the ear and mastoid process (H60-H95) Cataract and other disorders of lens in diseases classified elsewh Chorioretinal inflammation VIII. Diseases of the ear and mastoid process (H60-H95) Cataract and the respiratory system (J00-J99) Catalac arrest Paroxysmal tachycardia Intracerberal haemorrhage Portal vein thrombosis X. Diseases of the interprise tystem (K00-K33) Acute appendicits X. I. Diseases of the grees wystem (K00-K33) Acute appendicits X. II. Diseases of the ness rate as X. II. Diseases of the pressure area X. III. Diseases of the organic dust X. II. Diseases of the mean on the system and connective tis Osteopropais with pathological fracture Disorders of continuity of bone X. VII. Symptoms, signs and abnormal clinical and laboratory fin Somoolence, suppor and coma Convulsions X. M. Induce and upperson and coma Convulsions X. K. Indury, poisoning and certain other consequences of extern Fracture of lawades and upperson	ces nere ssue (M ndings, nal cau	ICI AE % 4.4 3.2 4.1 0.5 9.0 0.1 4.5 9.0 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0	Non-I AE % 4.2 3.1 0.4 3.4 0.0 3.4 3.2 1.0 0.1 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.0	CI HR(95% CI) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.6 (1.0-2.6) 1.2 (1.1-4.4) 5.7 (1.7-19.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.1 (1.0-1.3) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.8 (1.5-23.3) 2.4 (0.9-6.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.7 (1.1-2.5) 1.7 (1.1-2.5) 1.5 (1.1-1.9) 2.0 (1.5-2.6) 1.5 (1.1-1.9) 2.0 (1.5-2.6) 1.5 (1.1-1.9) 2.0 (1.5-2.6) 1.5 (1.1-1.9) 2.0 (1.5-2.6) 2.6 (1.5-2.6) 2.7 (1.5-2.6) 1.5 (1.1-1.9) 2.0 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.7 (1.5-2.6) 1.5 (1.1-1.9) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.7 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.7 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.6 (1.5-2.6) 2.7			HR sig.	PCR   sig. :	COR   sig. :	IC sig.
	Code A41 B02 B35 B59 E11 E24 E83 F30-F39 G40 G83 H28 H30 H67 I46 I47 I61 I81 J46 J47 I61 I81 J46 J46 J46 J46 K35 K35 K35 K35 K35 K35 K35 K35	Disease categories  I. Certain Infectious and parasitic diseases (A00-B99) Other sepsis Zoster [herpes zoster] Dermatophytosis Pneumocytosis(J17.3*) IV. Endocrine, nutritional and metabolic diseases (E00-E90) Type 2 diabetes mellitus Custing's syndrome Disorders of mineral metabolism V. Mental and behavioural disorders (F00-99) Dellirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (G00-G99) Eleirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the nervous system (G00-G99) Eleirum, not induced by alcohol and other psychoactive substance Mood [affective] disorders(F30-F39) V. Diseases of the eye and adnexa (H00-H59) Cataract and other disorders of lens in diseases classified elsewhere UII. Diseases of the eye and adnexa (H00-H59) Cutis media in diseases classified elsewhere IX. Diseases of the eirculatory system (I00-J99) Cardica arest Paroxysmal tachycardia Intracerberal heemorhage Portal vein thrombosis X. Diseases of the digestive system (M00-K33) Acute appendicits X.I. Diseases of the musculoskelatal system and connective tis Discreptores with pathological fracture Disorders of continuity of bone X. VIII. Systems of and adhormal clinical and laboratory fin Somnolence, stupor and coma Convulsions X. K. Injury, poisoning and certain other consequences of exercise Fracture of the max	ces nere ssue (M ndings, nal cau	ICI AE % 4.4 4.1 0.5 9.0 0.1 4.5 9.0 0.1 0.1 4.4 0.9 0.3 0.1 0.1 4.4 0.9 0.3 0.1 0.1 4.4 0.9 0.3 0.1 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.1 0.1 1.6 0.3 0.1 1.6 0.3 0.1 1.6 0.3 0.1 1.6 0.3 0.1 1.6 0.3 0.1 1.6 0.3 0.1 1.6 0.1 1.6 0.3 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.1 1.6 0.7 0.7 0.9 0.7 0.9 0.7 0.7 0.7 0.9 0.7 0.7 0.7 0.7 0.7 0.7 0.7 0.7	Non-I AE % 4.2 3.1 0.4 3.2 11.2 3.0 0.1 0.1 0.1 0.1 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.1 0.0 0.0	Cl HR(95% Cl) 1.2 (1.1-1.4) 1.3 (1.1-1.6) 1.3 (1.1-1.6) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.5 (1.3-1.8) 1.6 (1.3-1.9) 1.9 (1.5-2.5) 2.7 (1.3-5.3) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.3-1.8) 5.9 (1.2-29.4) 2.0 (1.7-2.3) 1.6 (1.1-2.4) 2.0 (1.7-2.3) 1.7 (1.1-5.5) 2.4 (1.1-5.1) 1.9 (1.3-2.8) 2.2 (1.5-3.1) 1.9 (1.1-2.6) 2.0 (1.5-2.6) 2.6 (1.5-4.6) 2.6 (1.5-4.6) 2.7 (1.5-4.6) 2.7 (1.5-4.6) 2.7 (1.5-4.6) 2.6 (1.5-4.6) 2.7 (1.5-4.6) 2.7 (1.5-4.6) 2.7 (1.5-4.6) 2.6 (1.5-4.6) 2.7			HR sig.	PCR   sig. :	COR   sig. :	IC sig.

#### FIGURE 2

Categorization of detected signals related to immune checkpoint inhibitor use from the nationwide claims database. (A) Well-known immunerelated adverse events. (B) Potential immune-related adverse events. AE, adverse events; HR, Hazard ratio; CI, Confidence interval; PCR, Proportional Claims Ratio; COR, Claims Odds Ratio; IC, Information Component. \* detected statistically significant results.

0.5 1.0 2.0 5.0 10.0 20.0

related AEs. The following associations were identified: i) Infectionrelated AEs-other types of sepsis, herpes zoster, dermatophytosis, and pneumocystosis; ii) Endocrine-related AEs- type 2 diabetes mellitus, Cushing's syndrome and disorders of mineral metabolism; iii) Mental and behavioral disorders-related AEs-delirium and mood disorders; iv) Eye and adnexa-related AEs-cataract, chorioretinal inflammation, and otitis media; v) Circulatory system-related AEs-cardiac arrest, intracerebral hemorrhage, and portal vein thrombosis; vi) Respiratory system-related AEs-status asthmaticus and hypersensitivity pneumonitis due to organic dust;

vii) Digestive system-related AEs-acute appendicitis; viii) Skin and subcutaneous tissue-related AEs-eccrine sweat disorders and decubitus ulcer; and viii) Bone disorders-related AEs-osteoporosis with pathological fracture, disorders in the continuity of the bone, fracture of the shoulder and upper arm, fracture of the femur, and fracture of the lower leg, including the ankle (Figure 2B).

# 3.4 Signal verification with hospital EMR database

Among the detected AE signals, signal verification for 17 targeted AEs was performed using additional hospital EMR database to address the limitation of the HIRA claims data (Figure 3; Supplementary Table S2). The incidence of detected AE signals was compared between population-level and hospital-level database. The signal verification was performed in two ways, using the diagnostic code and text mining.

From diagnostic codes in hospital-level EMR data (n=9,236; 836 ICI users and 8,400 non-ICI users), other types of sepsis (HR 2.3, 95% CI 1.5–3.6), nerve root and plexus disorders (HR 3.0, 95% CI 1.7–5.3), decubitus ulcer (HR 3.5, 95% CI 2.1–6.0), and convulsion (HR 2.8, 95% CI 1.4–5.7) were identified (Figure 3).

After defining targeted AEs by search term through text mining aside from using diagnostic codes (Supplementary Table S2), AE signals were verified from the hospital EMR database (Figure 3). In patients available for text mining (n=5118; 1,706 ICI users and 3,412 non-ICI users), the detected AEs were i) related to infections: other types of sepsis, herpes zoster, and pneumocystis; ii) related to metabolic disease: disorders in mineral metabolism; iii) related to mental disorders: delirium; iv) related to nervous disease: epilepsy; v) related to circulatory system: cardiac arrest: vi) related to skin and subcutaneous tissue: eccrine sweat disorders; and vii) related to symptom: somnolence and convulsion. These results indicate that AE signals detected from the NHI database were verified from the hospital EMR database, using both diagnostic codes and text mining.

## 4 Discussion

In the present study, we utilized both nationwide claims databases and hospital EMR to comprehensively monitor and detect signals of irAEs possibly associated with ICIs. The hospital EMR data, which includes structured and unstructured data such as clinical notes, was utilized to verify the detected irAE signals in the claim data. By integrating these two different real-world databases, we were able to identify irAE signals that were not well-established in the literature and assess their association with the use of ICIs. This integrated approach highlights the importance of utilizing both nationwide claims databases and hospital EMR data in real-world pharmacovigilance system. This comprehensive approach provides valuable insights into the safety profile of ICIs and contributes to the ongoing monitoring and management of irAEs in clinical practice.

Our analysis of claim data revealed the spectrum and incidences of well-known irAEs at the population level. The most common well-known irAEs observed were thyroid disorders, such as hypothyroidism, subclinical hypothyroidism, hyperthyroidism, and thyroiditis (20.8% in the ICI group vs. 7.6% in the non-ICI group; HR = 4.0, 95% CI 3.6-4.4). The incidence of thyroid irAEs in our study appeared to be higher than reported in phase III clinical trials, where the mean incidence was around 10.8% (23), but consistent with previous real-world studies, which have reported incidence rates ranging from 13% to 30% (24-26). In addition, our claim data analysis revealed other well-known irAEs across various organ systems, such as dermatologic AEs such as pruritus, dermatitis, and atopic dermatitis, musculoskeletal AEs such as systemic lupus erythematosus and other systemic involvement of connective tissue, gastrointestinal AEs such as hepatitis, respiratory AEs such as pneumonitis, ocular AEs such as iridocyclitis, and



FIGURE 3

Signal verification from the nationwide claims database and hospital electronic medical record database. AE, adverse events; HR, Hazard ratio; CI, Confidence interval,.

neurologic AEs such as meningitis (Figure 2). The incidence of these well-known typical irAEs was similar to previous studies involving PD-1/PD-L1 inhibitors (5, 27–30). Of note, the incidence of irAEs in respiratory system we detected was higher than that of previously reported (5, 31). These findings demonstrate the utility of nationwide claims databases in real-world AE monitoring and risk measurement.

Furthermore, our analysis unveiled new AE signals occurring more frequently in patients receiving ICIs compared to those receiving non-ICI agents. In the endocrine system, we identified type 2 diabetes mellitus (DM) (9.0% in the ICI group vs. 8.7% in the non-ICI group; HR = 1.2, 95% CI 1.1-1.4) and Cushing's syndrome (0.1% in the ICI group vs. 0.0% in the non-ICI group; HR = 5.7, 95% CI 1.7-19.8) as a new signal associated with ICI use. While ICIs are known to rarely cause type 1 DM (32, 33), their association with new-onset type 2 DM has not been well established. However, recent studies have indicated that ICIs may exacerbate pre-existing type 2 DM (33, 34) and increase the risk of developing incident diabetes (35), which aligns with our findings. Regarding Cushing's syndrome, it has been described in case reports of patients receiving ICIs (36, 37), but the specific details and relationship between Cushing's syndrome and ICIs have not been elucidated due to its rarity. These findings underscore the value of utilizing large-scale population-based claim data to uncover rare AE profiles. Nevertheless, caution is warranted in interpretation, as there is potential for increased steroid administration in ICI-treated patients due to irAEs. This may partially contribute to bias, leading to a higher prevalence of diabetes or Cushing 's disease in the ICI group compared to the non-ICI group.

In the nervous system, we detected an association between ICIs and epilepsy (3.8% in the ICI group vs. 3.0% in the non-ICI group; HR = 1.6, 95% CI 1.3–1.9), as well as somnolence/stupor/coma (0.6% in the ICI group vs. 0.5% in the non-ICI group; HR = 1.7, 95% CI 1.1-2.5). These findings were verified using hospital EMR data through text mining (for epilepsy, 0.8% in the ICI group vs. 0.3% in the non-ICI group, HR = 2.5, [95% CI: 1.8-3.5]; for somnolence/stupor/coma, 20.6% vs. 8.1%, HR = 2.6 [95% CI: 2.2-3.1)]. While these AE signals might be secondary to other well-known neurologic irAE such as encephalitis, they may also be associated with unrevealed irAE. In the circulatory system, we found new signals of cardiac arrest (4.4% in the ICI group vs. 2.7% in the non-ICI group; HR = 2.0, 95% CI 1.7-2.3), intracerebral hemorrhage (0.4% in the ICI group vs. 0.3% in the non-ICI group; HR = 2.0, 95% CI 1.2-3.3), and portal vein thrombosis (0.1% in the ICI group vs. 0.0% in the non-ICI group; HR: 5.6, 95% CI: 1.8-17.3) associated with ICI use. Thrombosis have been increasingly reported as an AE associated with ICIs, although data on its association with ICIs compared to traditional chemotherapy are conflicting (38-40). Mechanisms involving activated T cells, proinflammatory cytokines, and endothelial and platelet activation have been proposed (41-46).

Another notable finding was the association between ICIs and bone disorders, including osteoporosis with pathological fracture and fractures of various sites. After first case series describing skeletal irAEs associated with ICI in 2018 (46), another largescale pharmacovigilance analysis using the Food and Drug Association (FDA) Adverse Event Reporting System recently suggested a possible cause-effect relationship between serious vertebral fractures and ICI use in patients without apparent preexisting risk factors (47). Emerging evidence suggests that systemic activation of T cells leads to an osteoprotegerin ligand-mediated increase in osteoclastogenesis and bone loss. ICIs can enhance bone resorption by activating T cells (48), causing bone fragility and increasing the risk of fractures (49–51).

The verification of AE signals using the hospital EMR database demonstrated the complementarity of diagnostic codes and text mining. Text mining analysis has the potential of capturing AEs that clinicians have not yet assigned a diagnosis code to, or for which diagnostic codes could not assigned. The integration of these two approaches can enhance the detection of significant AE signals.

To the best of our knowledge, this population-based study is the first to investigate the nationwide incidence of AEs and compare the incidence of AEs between users of ICIs and conventional chemotherapy. Previous large-scale studies utilizing the FDA Adverse Event Reporting System or U.S. commercial insurance database have only reported the incidence of irAEs among ICI users in observational settings (48, 52). Moreover, our study included a large number of cancer patients treated with ICIs, surpassing the sample size of most randomized controlled trials (53). In addition, we applied multiple data mining indices and conducted a comprehensive review of the identified signals. If an AE signal was detected by multiple data mining indices, it was considered more robust compared to signals detected by a single index. The majority of signals reported in our study were detected using the HR, which reflects the time until the occurrence of an event. Consistent with our findings, another study that utilized a national health insurance claims database reported that the HR exhibited the highest sensitivity among the data mining indices (15). Therefore, it is recommended to apply multiple indices and compare the results, as it is challenging to determine the superior method of data mining (15, 54). Finally, we validated the signals identified from the hospital EMR database using two approaches: diagnostic codes and text mining.

Our study has several limitations. Firstly, due to the observation nature of this study, there is a possibility of misclassifying AEs. Since AEs were defined based on diagnostic codes, symptoms or nondiagnosed conditions may have gone undetected. Similarly, even if keywords were found in the hospital records, we cannot be certain if AEs actually occurred. Secondly, we were unable to assess the severity of AEs and detailed patient information such as cancer stage, performance status, and treatment history. Thirdly, it is conceivable that AEs associated with other anticancer medications may have been identified after transition to different anticancer medications within 18 months of initiating either ICI or non-ICI. Despite the potential for this bias, our intention was to capture signals for a sufficient duration after beginning study drug administration. The decision was motivated by the fact that various and significant irAEs such as endocrine AEs, colitis, nephritis or hepatitis can manifest at any time, even after the discontinuation of ICI therapy, and may wax and wane over time (55, 56). Fourthly, we only included PD1/PD-L1 inhibitors such as nivolumab, pembrolizumab, and atezolizumab. Hence, the

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safety profiles of other types of ICIs, such as CTLA-4 inhibitors, should be evaluated in the future. Finally, beyond signal detection and validation, which involved comparing the frequency of AEs between the ICI and non-ICI groups, we recognize the absence of in-depth analysis in this study. We are planning further research with more comprehensive investigations, including retrospective analyses using large-scale, long-term hospital databases, and analyses in prospective trials. These will aim to explore potential irAEs identified in our study, such as portal vein thrombosis and bone disorders.

## **5** Conclusion

This real-world data analysis utilizing both nationwide claims databases and hospital EMR, has demonstrated an effective approach for signal detection and evaluation of the irAEs. The development of an effective real-world pharmacovigilance system utilizing nationwide claims database can complement existing EMR systems and contribute to the early diagnosis and prompt treatment of rare irAEs. Further research and development of near real-time or earlier access to pharmacovigilance systems are warranted to enhance patient safety and improve outcomes.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: To utilize the Health Insurance Review and Assessment Service (HIRA) database, a formal application and approval process on the official website 'https://opendata.hira.or. kr/home.do.' was needed. Subsequent to the data export procedure, access to the dataset was granted on a limited and temporary basis, contingent upon a thorough review by the data-holding institution, with external network access restricted. For any inquiries or requests pertaining to dataset access, please direct them to 'https://opendata.hira.or.kr/home.do.

## **Ethics statement**

The studies involving humans were approved by Institutional Review Board of Asan Medical Center (IRB No. 2019-1300, 2019-1247). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

EK: Supervision, Writing – original draft, Writing – review & editing. Y-JK: Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review &

editing. JH: Conceptualization, Supervision, Writing – original draft. MK: Formal analysis, Writing – original draft. SL: Conceptualization, Methodology, Writing – review & editing. SS: Conceptualization, Supervision, Writing – review & editing. JM: Data curation, Formal analysis, Writing – original draft. JO: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. SP: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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# Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1295923/ full#supplementary-material

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