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ORIGINAL RESEARCH

Burden of Herpes Zoster in Individuals with Immunocompromised Conditions and Autoimmune Diseases in the Republic of Korea: A Nationwide Population-Based Database Study

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ABSTRACT

Introduction: To estimate herpes zoster (HZ) incidence rate (IR) and economic burden in individuals with immunocompromised conditions and autoimmune diseases (IC/AID) in the Republic of Korea (ROK).

Methods: The nationwide Health Insurance Review and Assessment Service database was used to identify HZ cases from 2016 to 2020 in ROK. HZ and non-HZ IC/AID cases were matched 1:3 using age, sex, institution, Charlson comorbidity index, IC/AID, and index date. Annual HZ IRs/1000 persons and 1-year HZ-associated all-cause direct medical costs for IC/AID cases were calculated.

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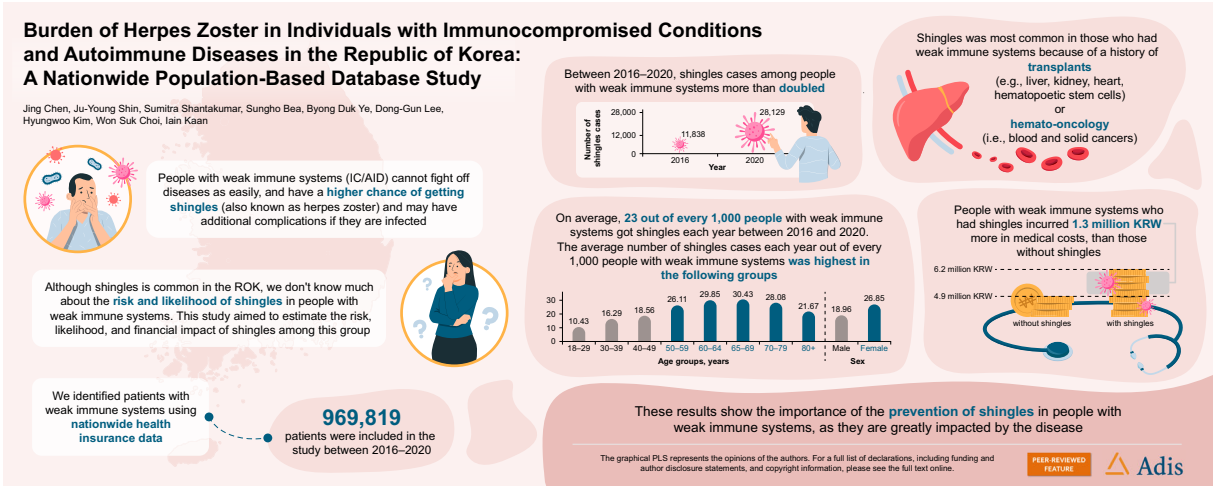
Results: Among 65,976 individuals with IC/AID (mean age 57.14 years [standard deviation 14.1]; 64.94% female), annual HZ IR (95% confidence interval) fluctuated from 2016 to 2020, averaging 23.41/1000 persons (22.21–24.62) and was higher in women (26.85 [25.40–28.31]) than men (18.96 [18.03–19.89]). IRs were highest in individuals aged ≥ 50 years, and in those with transplants (including solid organ and hematopoietic stem cell transplants; 37.12 [35.45–38.79]) and hemato-oncology conditions (35.5 [31.6–39.3]). Mean 12-month all-cause direct medical costs were higher in individuals with IC/AID and HZ (4,759,671 Korean Republic won [KRW]; approximately 4046 United States dollar [USD; according to the 2020 conversion rate from UNCTAD; 1 KRW = 0.00085 USD]) than those without HZ (3,786,658 KRW; 3219 USD).

Conclusion: Individuals with IC/AID have a substantial disease and economic burden from HZ in ROK, highlighting the need for appropriate HZ prevention measures in the IC/AID population.

Plain Language Summary:



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Keywords: Autoimmune diseases; Herpes zoster; Immunocompromised conditions; Republic of Korea

Key Summary Points

Why carry out the study?

We estimated the herpes zoster (HZ) incidence rate and economic burden in individuals with immunocompromised conditions and autoimmune diseases (IC/AID) in the Republic of Korea (ROK).

What was learnt from the study?

Between 2016 and 2020, the incidence of HZ among individuals with IC/AID was high across all age strata.

In individuals with IC/AID, mean all-cause direct medical costs were higher in those with HZ than without HZ

In ROK, individuals with IC/AID have a substantial disease and economic burden from HZ.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24534082.

INTRODUCTION

Herpes zoster (HZ), or shingles, is an illness which results in a painful rash caused by the reactivation of latent varicella-zoster virus (VZV) [1]. According to a worldwide systematic literature review, the pooled global incidence rate (IR) of HZ is 7.64 per 1000 persons [2] with the primary risk factors being advanced age and immunosuppression due to underlying disease or treatment (e.g., in patients with immunocompromised conditions [IC] or autoimmune diseases [AID]) [3, 4].

Globally, HZ and the associated complications are a significant burden in immunocompromised patients and lead to higher hospitalization and mortality rates [5, 6]. One common complication of HZ is postherpetic neuralgia (PHN), which is characterized by persistent pain for months to years after the HZ rash has resolved [7]. In immunocompromised patients, the infection tends to be more severe and have a longer duration [8, 9].

HZ has been an emerging public health concern in the Republic of Korea (ROK) in recent decades and numerous studies have reported that the disease burden of HZ in ROK continues to increase [10–14]. Local data identified an increase in the incidence rate per 1000 person-years among the general population from 2.67 in 2003 to 9.80 in 2015 [14]; the aging population and the increased prevalence of concurrent conditions or immunosuppression have been suggested as plausible explanations for this increasing incidence [14].

Given that patients with IC/AID are at high risk of HZ globally [6], measuring the disease burden of HZ among immunologically vulnerable populations in ROK is clinically important. This study therefore examined the trends in the incidence and recurrence rates of HZ among IC/AID populations and compared the healthcare resource utilization (HCRU) and HZ-associated medical costs of those with and without an HZ diagnosis, to provide insights into the burden of HZ in patients in ROK aged above 18 years with IC/AID between 2016 and 2020.

METHODS

Study Design and Population

We conducted a retrospective cohort study to estimate annual IR and recurrence rates of HZ in individuals aged ≥ 18 years with medical records of IC/AID during the study period (2016–2020), using the Health Insurance Review and Assessment Service (HIRA) database. Conditions related to IC/AID (e.g., diseases related to immunosuppression and

immunosuppressant use), listed in Supplementary Table S1, were selected on the basis of the available literature and opinions gathered from focus group interviews (FGI) with local clinical experts in gastroenterology, rheumatology, hemato-oncology, and infectious disease. The cohort entry date (CED) was defined as the date when the individual met one of the following inclusion criteria: (i) the date of diagnosis of each IC/AID condition based on the International Classification of Diseases, 10th revision (ICD-10) diagnosis codes [15]; or (ii) the date the patient turned 18 years old, whichever occurred later. The earliest CED was 1 January 2016. To ensure that HZ cases were new events, patients without medical claims records for at least 1 year before the CED, or those with a prior history of HZ or related complications before the CED in the HIRA database were excluded. Each individual included in the study was followed from the CED until either (i) in-hospital death or (ii) the end of the study period, whichever occurred first. Mortality data only includes in-hospital deaths.

Patients with incident HZ were identified as those who had received a HZ or HZ-related complications diagnosis (ICD-10 code B02) in hospital, outpatient, or emergency department settings and had received corresponding antiviral medication (acyclovir, valacyclovir, or famciclovir) within $\pm$ 7 days from the date of diagnosis of HZ during the follow-up period; in the sensitivity analysis, patients with incident HZ were identified by the HZ diagnosis code only. Recurrent HZ cases were defined as cases where a minimum of 1 year had passed from the previous HZ episode (i.e., if the subsequent HZ case was diagnosed within the 1 year after the date of diagnosis of the initial HZ case, the subsequent case was assumed as an identical episode).

PHN was defined as those who had made at least one claim for zoster with other nervous system involvement (ICD-10 code B02.2) or post-zoster neuralgia (ICD-10 code G53.0) between 90 days and 1 year after initial HZ diagnosis. Other complications of HZ infections (e.g., cutaneous [including soft skin tissue infections], disseminated, ocular, and neurologic complications) were defined at presentation within 30 days after the initial date of HZ diagnosis at any setting. Patients with HZ with no other claims in any healthcare setting for any complication during the designated period were categorized as "zoster without complication". The full list of ICD-10 codes used to identify patients with IC/AIDs and HZ complications is presented in Supplementary Table S1.

HZ Incidence and Recurrence

The average annual IRs of HZ in patients with IC/AID (per 1000 persons) with 95% confidence intervals (CI) were calculated from 2016 to 2020 as the number of HZ cases in a given year divided by the total number of patients with IC/AID in that year. The average annual recurrence rates of HZ in patients with IC/AID (per 1000 persons) were calculated from 2016 to 2020 as the number of recurrent HZ cases in a given year divided by the total number of patients with IC/AID and an initial HZ case in that year. These were calculated and stratified by age groups, sex, HZ-related complications, and IC/AIDs.

HCRU and All-Cause Medical Cost Assessment

To estimate the incremental HCRU and cost from HZ in patients with IC/AID and HZ compared with patients with IC/AID without HZ, 1:3 matching was performed between HZ cases and non-HZ controls among the IC/AID cohort by using the demographic information and clinical variables, including age groups (18–29, 30–39, 40–49, 50–59, 60–64, 65–69, 70–79, 80+ years), sex, type of medical institution (tertiary hospital, general hospital, primary hospital, and clinic), individual IC/AID condition, baseline Charlson comorbidity index (CCI) score, and the index date ($\pm$ 90 days; Supplementary Fig. S1). IC/AID as a categorical variable within 1-year prior to the index date was excluded in the calculation of the CCI score (i.e., 0, 1, 2, and $\geq$ 3). The index date for patients with HZ was defined as 7 days prior to the first date of HZ diagnosis; the period of 7 days was set by considering the accessibility of

medical institutions in ROK after consultation with clinical experts.

HCRU and all-cause medical cost per patient was assessed for patients with IC/AID with and without HZ from the index date through the 12-month follow-up period. HCRU and medical costs included costs incurred in the processing of HZ diagnosis, such as analgesics for symptoms of HZ, or HZ diagnostic tests.

All-cause medical costs included all medical costs, regardless of the reason for the hospitalization or visit. All-cause direct medical costs were estimated by the costs for treating all diseases during the follow-up period. This included only medical costs which were claimable by the National Health Insurance Service (NHIS) as captured in the HIRA database and excluded the cost of over-the-counter or non-reimbursed procedures. The NHIS is a public health insurance system covering the majority of citizens and residents in ROK, which requires those insured to pay income-based premiums. As the single insurer, NHIS reimburses healthcare providers on the basis of billing records, which typically bill their services using a fee-for-service system, although costs vary between different healthcare providers [16–18].

All-cause indirect medical costs were estimated by costs of lost workdays as follows: (average length of hospital stays or days of outpatient visit of the working-age population) × (average employment rate) × (average daily income), with the working-age population defined as people 18–65 years of age. The employment rate and average daily income were determined using the annual data from the Korean Statistical Information Service.

HCRU and all-cause medical cost among patients with IC/AID with and without HZ for the 12-month follow-up period from the index date was estimated. Next, we measured the excess burden of patients with IC/AID and HZ relative to patients with IC/AID without HZ by comparing the annual incremental HCRU and costs calculated from the difference between the two groups. The cost ratio of HCRU and all-cause healthcare cost was also estimated and adjusted for demographic information and clinical variables using a generalized linear model.

Ethics/Ethical Approval

This study was performed in accordance with the ethical principles outlined in the Helsinki Declaration of 1964, its later amendments, and all applicable laws and regulations governing research involving human participants. Approval for this study was obtained from the Sungkyunkwan University (SKKU) Ethics Committee (Protocol number SKKU 2021–03-008) and followed the guidelines and recommendations provided by the aforementioned ethics committee.

As the databases used for this retrospective claims analysis study consisted of Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant de-identified data, informed consent for publication was not required. Confidentiality and anonymity are implied owing to the nature of this database analysis.

RESULTS

Study Population

A total of 1,527,072 patients with IC/AID aged ≥ 18 years in ROK were considered eligible for inclusion in the study between 2016 and 2020.

Of these patients, 557,243 were later excluded from the study cohort on the basis of the exclusion criteria: 20,316 aged below 18 years during the study period; 7 with missing age; 98,827 diagnosed with HZ before CED; 176,642 without continuous enrolment during the baseline period of at least 1 year before cohort entry; 1322 diagnosed with solely documented cases of liver cirrhosis and without decompensated events; 108,357 diagnosed with two or more IC/AID conditions on CED and 151,772 with less than 1 year of follow-up. Eligible patients for the study cohort consisted of 969,819 patients aged ≥ 18 years with IC/AID between 2016 and 2020 (Supplementary Fig. S2).

Baseline Characteristics of Immunocompromised Patients

Prior to matching, the mean age (standard deviation [SD]) of the "IC/AID with HZ" group (57.40 [14.14]) was higher than that of the "IC/AID without HZ" group (53.60 [16.47]). Among IC/AID with HZ and IC/AID without HZ groups, 64.92% and 55.61% of patients were female, respectively. The mean (SD) value of CCI was 1.16 (1.44) for the IC/AID with HZ group, and 0.92 (1.39) for the IC/AID without HZ group ($p < 0.0001$; Table 1).

Rheumatoid arthritis was the most common IC/AID condition in both IC/AID with HZ and without HZ groups. Individuals with IC/AID and HZ ($n = 65,976$) were matched 1:3 to patients with IC/AID without HZ ($n = 197,062$) (Supplementary Fig. S2). After matching, the cohorts were well balanced with regard to age, sex, medical institution, CCI, and IC/AID conditions (Table 1).

HZ Incidence and Recurrence

Main Analysis

From 2016 to 2020, the total number of patients with IC/AID more than doubled from 557,521 to 1,229,948 (Table 2). Accordingly, the number of patients with HZ and IC/AID also more than doubled from 11,838 in 2016 to 28,129 in 2020. The annual IR (95% CI) per 1000 persons fluctuated from 2016 to 2020; it was at its lowest in 2016 (21.23 [20.86–21.62]) and peaked in 2018 (24.52 [24.21–24.84]), averaging at 23.41 (22.21–24.62) throughout the study period.

HZ was more common in female patients with IC/AID (IR [95% CI] 26.85 [25.40–28.31]) than in male patients with IC/AID (18.96 [18.03–19.89]). In addition, the IR of HZ among patients with IC/AID remained high across all age strata, ranging from 10.43 (9.88–10.97) among individuals aged 18–29 years to 30.43 (29.17–31.69) among individuals aged 65–-69 years. Overall, incidence was highest in patients above 50 years of age. When stratified by etiology of IC/AID, the IR (95% CI) of HZ per 1000 persons was highest in patients with transplants (including both solid organ and hematopoietic stem cell transplants) (37.12 [35.45–38.79]), followed by patients with hemato-oncology conditions (35.47 [31.62–39.32]; Table 2).

Forty-eight percent of the patients with HZ (14,683/30,562) did not experience HZ complications (15.84 [14.95–16.72]). Among the cases where complications occurred, "other complications"-related cases (3.84 [1.95–5.73]) were the most common, followed by PHN (1.87 [1.42–2.31]; Table 2). The category "other complications" (ICD-10 code B02.8) includes zoster which has spread to other organs and does not fall under ICD-10 codes B02.0–B02.7 or B02.9 (zoster without complications).

The trend of HZ recurrence was generally homogenous to that of HZ incidence. The average recurrence rate per 1000 persons across the study period was 1.71 (0.30–3.11). The recurrence rate was highest among women (2.20 [1.09–3.31]), individuals aged 60–64 years (2.51 [1.26–3.76]), and individuals with transplants (3.35 [2.54–4.17]; Table 3).

Sensitivity Analysis

Patients with incident and recurrent HZ were identified in the sensitivity analysis by the HZ diagnosis code only and need not have received antiviral medication within 1 week of HZ diagnosis. Hence, the number of cases, IRs, and recurrence rates were relatively higher in the sensitivity analysis compared with the main analysis. However, the trends of HZ incidence and recurrence rates among patients with IC/AID in both analyses were largely consistent (Tables 2 and 3; Supplementary Tables S2 and S3).

HCRU and All-Cause Medical Cost Assessment

HZ Healthcare Burden

Compared to patients with IC/AID without HZ, patients with IC/AID and HZ had higher HCRU during the 12-month observation period in all HCRU categories (number of outpatient visits, emergency room visits, inpatient visits, and length of hospitalizations; Table 4). The ratio of healthcare utilization (95% CI) for all patients

Table 1 Baseline characteristics of patients with IC/AID with or without HZ before and after matching

Characteristics	Before matching			After matching (up to 1:3)		
	IC/AID with HZ *N* = 66,226; *n* (%)	IC/AID without HZ *N* = 903,593; *n* (%)	ASD[a]	IC/AID with HZ *N* = 65,976; *n* (%)	IC/AID without HZ *N* = 197,062; *n* (%)	ASD[a]
Age group, years						
Mean (SD)	57.40 (14.14)	53.60 (16.47)		57.14 (14.13)	57.06 (14.29)	
18–29	2580 (3.90)	83,862 (9.28)	5.38	2559 (3.88)	7612 (3.86)	0.02
30–39	5372 (8.11)	108,666 (12.03)	4.64	5350 (8.11)	15,981 (8.11)	0.00
40–49	9270 (14.00)	156,670 (17.54)	3.34	9246 (14.01)	27,635 (14.02)	0.01
50–59	18,715 (28.26)	217,367 (24.06)	4.20	18,673 (28.30)	55,864 (28.35)	0.05
60–64	9063 (13.68)	94,690 (10.48)	3.20	9012 (13.66)	26,895 (13.65)	0.01
65–69	7593 (11.47)	77,039 (8.53)	2.94	7551 (11.45)	22,521 (11.43)	0.02
70–79	10,666 (16.11)	118,250 (13.09)	3.02	10,632 (16.11)	31,760 (16.12)	0.01
80+	2967 (4.48)	47,049 (5.21)	0.73	2953 (4.48)	8794 (4.46)	0.02
Sex						
Male	23,229 (35.08)	401,132 (44.39)	9.31	23,134 (35.06)	69,069 (35.05)	0.01
Female	42,997 (64.92)	502,461 (55.61)	9.31	42,842 (64.94)	127,993 (64.95)	0.01
Medical institution						
Tertiary hospital	17,780 (26.85)	185,139 (20.49)	21.12	17,716 (26.85)	52,902 (26.85)	0.00
General hospital	10,084 (15.23)	135,321 (14.98)	20.08	10,021 (15.19)	29,834 (15.14)	0.05
Primary hospital	4404 (6.65)	64,966 (7.19)	4.12	4349 (6.59)	12,857 (6.52)	0.07
Clinic	33,958 (51.28)	518,167 (57.35)	45.33	33,890 (51.37)	101,469 (51.49)	0.12
CCI score						
Mean (SD)	1.16 (1.44)	0.92 (1.39)		1.16 (1.44)	1.16 (1.44)	
0	27,556 (41.61)	486,251 (53.81)	9.40	27,496 (41.68)	82,303 (41.77)	0.09
1	23,222 (35.06)	231,897 (25.66)	0.03	23,150 (35.09)	69,202 (35.12)	0.03
2	7490 (11.31)	101,957 (11.28)	2.78	7442 (11.28)	22,143 (11.24)	0.04
3+	7958 (12.02)	83,488 (9.24)	12.20	7888 (11.96)	23,414 (11.88)	0.08
IC/AID						
Diseases related to immunosuppression						
Human immunodeficiency virus infection	841 (1.27)	11,370 (1.26)	0.01	811 (1.23)	2384 (1.21)	0.02
Hemato-oncology conditions	5007 (7.56)	46,786 (5.18)	2.38	4980 (7.55)	14,815 (7.52)	0.03

Table 1 continued

Characteristics	Before matching			After matching (up to 1:3)		
	IC/AID with HZ *N* = 66,226; *n* (%)	IC/AID without HZ *N* = 903,593; *n* (%)	ASD[a]	IC/AID with HZ *N* = 65,976; *n* (%)	IC/AID without HZ *N* = 197,062; *n* (%)	ASD[a]
Myelodysplastic syndrome	244 (0.37)	4325 (0.48)	0.11	219 (0.33)	604 (0.31)	0.02
Decompensated liver cirrhosis	1185 (1.79)	32,881 (3.64)	1.85	1169 (1.77)	3459 (1.76)	0.01
Diseases related to immunosuppressant use						
Crohn's disease	593 (0.90)	8547 (0.95)	0.05	575 (0.87)	1672 (0.85)	0.02
Ulcerative colitis	3054 (4.61)	45,677 (5.06)	0.45	3042 (4.61)	9041 (4.59)	0.02
Rheumatoid arthritis	33,994 (51.33)	392,852 (43.48)	7.85	33,991 (51.52)	101,968 (51.74)	0.22
Psoriasis	15,225 (22.99)	282,551 (31.27)	8.28	15,222 (23.07)	45,611 (23.15)	0.08
Systemic lupus erythematosus	1558 (2.35)	12,309 (1.36)	0.99	1521 (2.31)	4421 (2.24)	0.07
Ankylosing spondylitis	2431 (3.67)	43,561 (4.82)	1.15	2407 (3.65)	7144 (3.63)	0.02
Aplastic anemia	442 (0.67)	6907 (0.76)	0.09	423 (0.64)	1208 (0.61)	0.03
Transplants (including solid organ and hematopoietic stem cell transplants)	1652 (2.49)	15,827 (1.75)	0.74	1616 (2.45)	4735 (2.4)	0.05

AID autoimmune disease, *ASD* absolute standardized difference, *CCI* Charlson comorbidity Index, *HZ* herpes zoster, *IC* immunocompromised condition, *SD* standard deviation

[a]Absolute standardized difference is considered a good match when the absolute value of the standardized difference is less than 0.1 for the majority of matching factors

with HZ was 1.28 (1.28–1.29) in outpatient visits, 1.32 (1.31–1.33) in emergency room visits, 1.31 (1.30–1.32) in inpatient visits, and 1.14 (1.14–1.15) in the length of hospitalizations. The incremental HCRU attributable to HZ in each resource category increased for patients with HZ-related complications, and substantially increased for patients with HZ and PHN complications (Table 4). The ratio of outpatient visits (95% CI) was significantly higher in patients with HZ and PHN, with a mean of 25.43 additional claims for services compared with patients without HZ (1.61 [1.60–1.62]) through the 12 months following diagnosis.

All-Cause Total, Direct, and Indirect Medical Costs

Compared with the IC/AID without HZ group, the IC/AID with HZ group had significantly higher all-cause total medical cost (cost ratio 1.19 [1.18–1.20]), and an additional 1,338,475 Korean Republic won (KRW; 1138 United States dollar [USD] according to the 2020 conversion rate from UNCTAD [19]; 1 KRW = 0.00085 USD) was incurred per patient during the 12-month observation period. Among patients with HZ and complications, patients with PHN were the primary cost drivers with incremental all-cause total medical costs over 40% of that of patients without HZ during the 12-month observation period (1.42 [1.37–1.47]), incurring an

Table 2 Trend of HZ incidence rates per 1000 persons among patients with IC/AID in the Republic of Korea from 2016 to 2020, stratified by year, age, sex, IC/AIDs, and HZ-related complications

	Number of patients with IC/AID, *n*	Number of HZ cases; *n*[a, b]	Annual incidence rates; *n* (95% CI[c])[d,e]
Year			
2016	557,521	11,838	21.23 (20.86–21.62)
2017	765,793	18,486	24.14 (23.80–24.49)
2018	941,930	23,100	24.52 (24.21–24.84)
2019	1,101,371	26,759	24.30 (24.01–24.59)
2020	1,229,948	28,129	22.87 (22.61–22.87)
Average	919,313	21,662	23.41 (22.21–24.62)
Age group, years[f]			
18–29	68,397	720	10.43 (9.88–10.97)
30–39	100,474	1654	16.29 (15.35–17.23)
40–49	148,169	2787	18.56 (17.24–19.88)
50–59	217,792	5715	26.11 (24.83–27.39)
60–64	106,611	3203	29.85 (28.37–31.34)
65–69	84,722	2587	30.43 (29.17–31.69)
70–79	132,640	3721	28.08 (26.27–29.89)
80+	60,506	1276	21.67 (19.93–23.42)
Sex[f]			
Male	400,841	7633	18.96 (18.03–19.89)
Female	518,472	14,030	26.85 (25.40–28.31)
IC/AID[f]			
Aplastic anemia	11,749	308	26.67 (24.50–28.83)
Decompensated liver cirrhosis	35,079	533	15.19 (13.74–16.64)
Hemato-oncology conditions	59,356	2051	35.47 (31.62–39.32)
Human immunodeficiency virus infection	12,366	258	20.92 (19.57–22.26)
Myelodysplastic syndrome	8,570	219	26.16 (23.50–28.81)
Ankylosing spondylitis	62,157	1188	18.74 (17.01–20.48)
Crohn's disease	14,254	278	19.36 (17.17–21.56)
Psoriasis	274,803	5172	18.46 (16.80–20.12)
Rheumatoid arthritis	431,343	11,562	26.55 (24.87–28.24)
Systemic lupus erythematosus	34,834	1072	30.84 (29.72–31.96)

Table 2 continued

	Number of patients with IC/AID, *n*	Number of HZ cases; *n*[a, b]	Annual incidence rates; *n* (95% CI[c])[d,e]
Transplants (including solid organ and hematopoietic stem cell transplants)	26,501	979	37.12 (35.45–38.79)
Ulcerative colitis	50,526	1101	21.46 (19.62–23.30)
HZ complications[f]			
Cutaneous		1202	1.29 (1.21–1.38)
Disseminated		329	0.36 (0.34–0.39)
Ocular		812	0.88 (0.83–0.93)
Neurologic		270	0.29 (0.27–0.31)
Postherpetic neuralgia		1793	1.87 (1.42–2.31)
Other complications		4493	3.84 (1.95–5.73)
All complications		6980	7.58 (7.22–7.93)
No complications		14,683	15.84 (14.95–16.72)

AID autoimmune disease, *CI* confidence interval, *HZ* herpes zoster, *IC* immunocompromised condition

[a]HZ defined as HZ diagnostic codes plus antiviral medications (acyclovir, valacyclovir, or famciclovir) dispensed within ± 7 days of the HZ diagnosis date in the main analysis

[b]The average number of HZ cases was calculated as the total number of HZ cases in each subgroup divided by the duration of the study period (5 years)

[c]95% confidence intervals were calculated by using exact binomial method

[d]Denominator represents the sum of the number of patients with IC/AID

[e]Per 1000 persons

[f]Values in these sections are averaged across the 5-year period of the study

additional burden of 3,090,973 KRW (2627 USD) per patient (Table 5).

During the 12-month observation period, patients in the IC/AID with HZ group incurred significantly higher direct medical costs (1.18 [1.17–1.19]), resulting in the additional cost of 973,013 KRW (827 USD) per patient (Supplementary Table S4). Whereas in the inpatient setting, adjusted cost ratios of direct medical costs for patients in the IC/AID with HZ group were slightly lower than that of the IC/AID without HZ group (0.95 [0.93–0.97]). Significant incremental direct medical costs were incurred in patients with HZ and PHN compared to matched patients in the IC/AID without HZ group. Differences in mean direct medical costs were 2,343,338 KRW (1992 USD) per patient and the cost ratio of direct medical costs was 1.40 (1.35–1.45).

During the 12-month observation period, patients in the IC/AID with HZ group incurred significantly higher indirect medical costs (cost ratio 1.25 [1.24–1.26]), resulting in the additional cost of 365,462 KRW (311 USD) per patient (Supplementary Table S5). In the inpatient setting, however, there was no significant difference in indirect medical cost between IC/AID with HZ and IC/AID without HZ groups. The indirect medical cost for patients with HZ and PHN was approximately 1.65 times that of patients in the IC/AID without HZ group (1.65 [1.60–1.70]), incurring an additional burden of 747,635 KRW (635 USD) per patient.

Table 3 Trend of HZ recurrence rates per 1000 persons among patients with IC/AID in the Republic of Korea from 2017 to 2020, stratified by year, age, sex, and IC/AID

	Number of patients with IC/AID, *n*	Number of recurrent cases, *n*[a, b]	Annual recurrence rates, *n* (95% CI)[c, d]
Calendar year			
2017	765,793	403	0.53 (0.48–0.58)
2018	941,930	1176	1.25 (1.18–1.32)
2019	1,101,371	2182	1.98 (1.90–2.07)
2020	1,229,948	3130	2.54 (2.46–2.64)
Average	1,009,761	1723	1.71 (0.30–3.11)
Age group, years[e]			
18–29	68,397	105	0.44 (0.23–0.66)
30–39	100,474	199	0.96 (0.42–1.49)
40–49	148,169	459	1.23 (0.56–1.91)
50–59	217,792	296	1.93 (0.98–2.88)
60–64	106,611	232	2.51 (1.26–3.76)
65–69	84,722	314	2.50 (1.15–3.84)
70–79	132,640	86	2.14 (1.06–3.21)
80+	60,506	105	1.23 (0.87–1.59)
Sex[e]			
Male	400,841	471	1.07 (0.52–1.61)
Female	518,472	1252	2.20 (1.09–3.31)
IC/AID[e]			
Aplastic anemia	11,749	22	1.67 (1.36–1.98)
Decompensated liver cirrhosis	35,079	22	0.56 (0.38–0.73)
Hemato-oncology conditions	59,356	193	2.99 (2.45–3.53)
Human immunodeficiency virus infection	12,366	24	1.88 (1.49–2.26)
Myelodysplastic syndrome	8,570	17	1.79 (1.50–2.08)
Ankylosing spondylitis	62,157	84	1.25 (0.91–1.59)
Crohn's disease	14,254	19	1.27 (0.80–1.75)
Psoriasis	274,803	365	1.20 (0.85–1.54)
Rheumatoid arthritis	431,343	973	2.06 (1.51–2.60)
Systemic lupus erythematosus	34,834	107	2.81 (2.03–3.60)
Transplants (including solid organ and hematopoietic stem cell transplants)	26,501	94	3.35 (2.54–4.17)

Table 3 continued

	Number of patients with IC/AID, *n*	Number of recurrent cases, *n*[a, b]	Annual recurrence rates, *n* (95% CI)[c, d]
Ulcerative colitis	50,526	85	1.54 (1.13–1.96)

AID autoimmune disease, *CI* confidence interval, *HZ* herpes zoster, *IC* immunocompromised condition

[a]HZ defined as HZ diagnostic codes plus antiviral medications (acyclovir, valacyclovir, or famciclovir) dispensed within ± 7 days of the HZ diagnosis date in the main analysis

[b]The average number of recurrent cases was calculated as the total number of recurrent cases in each subgroup divided by duration of 4 years. Recurrent cases of HZ were defined as the subsequent cases of HZ that have passed after a minimum of 1 year from the previous HZ episode

[c]Denominator represents the sum of the number of patients with IC/AID

[d]Per 1000 persons

[e]Values in these sections are averaged across 4 years

DISCUSSION

In this study, we estimated the annual and average annual incidence, recurrence, and economic burden of HZ among patients with IC/AID aged ≥ 18 years in ROK. The average HZ IR (95% CI) per 1000 persons among patients with IC/AID was 23.41 (22.21–24.62) and remained high across all age strata. The high HZ IRs among patients with IC/AID during the study period could be partially associated with the exclusive availability of live-attenuated zoster vaccines in ROK, which are contraindicated for patients with IC/AID because of the risk of developing HZ and other severe outcomes, including death [20–22].

Numerous studies have noted that individuals with infectious diseases bear a higher risk of HZ and observed an increased incidence of HZ during the COVID-19 pandemic [23, 24]. In contrast to this, in ROK, the annual incidence of HZ decreased in 2020 compared to 2019, despite 2020 being the year the World Health Organization announced the COVID-19 pandemic. The observed decrease in the incidence of many infectious diseases, including HZ, during the COVID-19 pandemic could be attributed to multiple factors, such as a decreased transmission of infectious diseases due to social distancing measures and changes in healthcare-seeking behavior (as patients with mild cases of HZ were perhaps less likely to visit clinics during the COVID-19 pandemic) [25, 26].

Data on the incidence of HZ recurrence are critical for economic analyses of vaccination programs; however, available data are limited [27]. Previous studies on the risk of recurrence have small sample sizes, or use data from old-fashioned databases where population composition, condition, and case definitions vary, making comparisons across studies difficult [28–31]. In our recurrence analysis, identification of the initial HZ episode and HZ recurrence required both a diagnostic code and a prescription of antiviral medications to ensure the diagnostic validity of HZ using the latest database, allowing for a clearer interpretation of the data. A single episode of HZ may require multiple visits to healthcare facilities, especially if a patient has any long-term complications. There is no well-established time point to differentiate between an initial and recurrent HZ episode. Therefore, based on the FGI conducted with local clinical experts, a cutoff of 1 year after a HZ episode was used in this study to minimize the overestimation of the number of patients with recurrent episodes of HZ. Our findings suggest a linear increase of recurrence from 2017 to 2020 in ROK patients with IC/AID, which was especially notable in female patients with IC/AID aged ≥ 50 years.

In addition, we estimated and compared the all-cause HCRU and total medical costs at

Table 4 Healthcare resource utilization associated with HZ in patients with IC/AID during the 12-month follow-up period

	IC/AID with HZ		Matched group[a]		Incremental utilization[b]		Ratio (95% CI)[c]	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean	Mean	Crude	Adjusted[d]
Overall HZ[e]								
Number of outpatient visits, *n*	39.34 (34.32)	30 (31)	29.41 (29.8)	22 (26)	9.93	8	1.34 (1.34–1.34)	1.28 (1.28–1.29)
Number of hospitalizations, *n*	0.94 (2.29)	0 (1)	0.72 (2.17)	0 (1)	0.22	0	1.30 (1.29–1.32)	1.31 (1.30–1.32)
Length of hospitalization, days	8.15 (28.68)	0 (4)	7.39 (34.23)	0 (1)	0.76	0	1.10 (1.10–1.11)	1.14 (1.14–1.15)
Number of ER visits, *n*	1.45 (3.98)	0 (1)	1.09 (3.54)	0 (1)	0.36	0	1.33 (1.32–1.34)	1.32 (1.31–1.33)
HZ with complications*								
Number of outpatient visits, *n*	44.81 (38.58)	35 (35)	30.41 (30.54)	23 (27)	14.40	12	1.47 (1.47–1.48)	1.39 (1.38–1.39)
Number of hospitalizations, *n*	1.05 (2.41)	0 (1)	0.75 (2.23)	0 (1)	0.30	0	1.41 (1.38–1.43)	1.41 (1.39–1.43)
Length of hospitalization, days	9.28 (30)	0 (6)	7.85 (35.4)	0 (1)	1.43	0	1.18 (1.18–1.19)	1.23 (1.22–1.24)
Number of ER visits, *n*	1.58 (4.04)	0 (2)	1.1 (3.2)	0 (1)	0.48	0	1.43 (1.41–1.45)	1.41 (1.39–1.43)
HZ with complications with exception of PHN*								
Number of outpatient visits, *n*	40.68 (35.35)	31 (32)	29.51 (29.81)	22 (26)	11.16	9	1.38 (1.37–1.38)	1.31 (1.30–1.31)
Number of hospitalizations, *n*	0.9 (2.24)	0 (1)	0.7 (2.16)	0 (1)	0.20	0	1.29 (1.27–1.31)	1.30 (1.27–1.32)
Length of hospitalization, days	7.84 (28.73)	0 (4)	7.16 (33.47)	0 (1)	0.68	0	1.09 (1.09–1.10)	1.14 (1.13–1.14)
Number of ER visits, *n*	1.37 (3.34)	0 (1)	1.05 (3.09)	0 (1)	0.32	0	1.30 (1.28–1.32)	1.29 (1.27–1.31)
HZ with PHN								
Number of outpatient visits, *n*	58.88 (45.24)	48 (42)	33.46 (32.74)	25 (29)	25.43	23	1.76 (1.75–1.77)	1.61 (1.60–1.62)
Number of hospitalizations, *n*	1.57 (2.85)	1 (2)	0.92 (2.44)	0 (1)	0.65	1	1.71 (1.67–1.76)	1.71 (1.66–1.76)

Table 4 continued

	IC/AID with HZ		Matched group[a]		Incremental utilization[b]		Ratio (95% CI)[c]	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean	Mean	Crude	Adjusted[d]
Length of hospitalization, days	14.2 (33.51)	1 (13)	10.2 (41.24)	0 (2)	4.00	1	1.39 (1.38–1.40)	1.46 (1.44–1.47)
Number of ER visits, *n*	2.3 (5.77)	1 (3)	1.28 (3.53)	0 (1)	1.02	1	1.80 (1.76–1.84)	1.74 (1.70–1.78)
HZ without complications[*]								
Number of outpatient visits, *n*	36.33 (31.32)	28 (28)	28.86 (29.37)	21 (26)	7.47	7	1.26 (1.26–1.26)	1.24 (1.24–1.24)
Number of hospitalizations, *n*	0.87 (2.21)	0 (1)	0.7 (2.14)	0 (1)	0.17	0	1.24 (1.23–1.26)	1.25 (1.24–1.27)
Length of hospitalization, days	7.53 (27.91)	0 (3)	7.14 (33.57)	0 (1)	0.38	0	1.05 (1.05–1.06)	1.09 (1.09–1.1)
Number of ER visits, *n*	1.38 (3.94)	0 (1)	1.08 (3.72)	0 (1)	0.30	0	1.27 (1.26–1.29)	1.27 (1.26–1.28)

AID autoimmune disease, *CCI* Charlson comorbidity index, *CI* confidence interval, *HZ* herpes zoster, *ER* emergency room, *HZ* herpes zoster, *IC* immunocompromised condition, *IQR* interquartile range, *PHN* postherpetic neuralgia, *SD* standard deviation

[a]Matched according to age group, sex, CCI, and prevalence period of IC/AID

[b]Differences of healthcare resource utilization between IC/AID with HZ and matched group

[c]Estimated by generalized linear model with Poisson distribution

[d]Adjusted for age group, sex, medical institution on the index date, CCI score, common comorbidities, medical costs per patient, number of outpatient visits, number of hospitalizations, and mean length of stay per hospitalization within 1 year prior to the index date

[e]Overall HZ includes individuals diagnosed with HZ with PHN or HZ without complications among individuals with IC/AID and their matched individuals

[f]HZ with complications includes patients diagnosed with both HZ and complications among patients with IC/AID and their matched individuals

[g]HZ without complications included patients diagnosed with both HZ and B02.9 or only HZ among patients with IC/AID and their matched individuals

*Complications include cutaneous, disseminated, ocular, neurologic, and other complications

Table 5 All-cause total medical costs associated with HZ among patients with IC/AID during the 12-month follow-up period

	IC/AID with HZ, ₩		Matched group, ₩[a]		Incremental cost, ₩[b]		Cost ratio (95% CI)[c]	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean	Median	Crude	Adjusted[d]
Overall HZ[e]								
12-month total medical costs per patient	6,226,140 (11,746,593)	2,953,357 (4,801,895)	4,887,665 (10,545,435)	2,056,380 (3,729,624)	1,338,475	896,977	1.21 (1.20–1.22)	1.19 (1.18–1.20)
12-month total direct medical costs	4,759,671 (11,243,296)	1,536,395 (3,390,185)	3,786,658 (10,126,378)	1,032,975 (2,425,310)	973,013	503,420	1.20 (1.18–1.21)	1.18 (1.17–1.19)
12-month total indirect medical costs	1,466,469 (2,002,394)	981,507 (2,140,564)	1,101,007 (1,644,953)	615,230 (1,584,005)	365,462	366,277	1.28 (1.27–1.29)	1.25 (1.24–1.26)
HZ with complications*								
12-month total medical costs per patient	6,594,608 (11,870,943)	3,297,635 (5,232,934)	4,875,564 (10,187,021)	2,047,720 (3,766,367)	1,719,044	1,249,916	1.29 (1.27–1.31)	1.24 (1.22–1.26)
12-month total direct medical costs	5,059,781 (11,305,412)	1,827,935 (3,780,550)	3,837,474 (9,796,819)	1,079,240 (2,504,520)	1,222,306	748,695	1.25 (1.23–1.28)	1.22 (1.20–1.24)
12-month total indirect medical costs	1,534,827 (2,243,640)	923,564 (2,281,552)	1,038,089 (1,617,381)	489,159 (1,516,140)	496,738	434,405	1.42 (1.40–1.44)	1.35 (1.33–1.37)
HZ with complications with exception of PHN*								
12-month total medical costs per patient	6,023,894 (10,726,458)	3,020,137 (4,700,594)	4,707,882 (9,835,707)	2,032,280 (3,671,404)	1,316,012	987,857	1.22 (1.19–1.24)	1.19 (1.17–1.21)
12-month total direct medical costs	4,518,332 (10,193,049)	1,570,000 (3,198,010)	3,625,465 (9,430,928)	1,032,080 (2,386,220)	892,867	537,920	1.18 (1.16–1.21)	1.16 (1.14–1.18)
12-month total indirect medical costs	1,505,561 (2,085,079)	1,011,109 (2,210,504)	1,082,416 (1,606,731)	598,484 (1,564,802)	423,145	412,625	1.33 (1.31–1.36)	1.29 (1.27–1.30)
HZ with PHN								
12-month total medical costs per patient	8,538,555 (14,971,969)	4,449,571 (6,890,280)	5,447,582 (11,285,215)	2,106,103 (4,121,175)	3,090,973	2,343,468	1.50 (1.44–1.55)	1.42 (1.37–1.47)

Table 5 continued

	IC/AID with HZ, ₩		Matched group, ₩[a]		Incremental cost, ₩[b]		Cost ratio (95% CI)[c]	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean	Median	Crude	Adjusted[d]
12-month total direct medical costs	6,904,044 (14,314,396)	2,866,685 (5,452,040)	4,560,707 (10,922,820)	1,245,150 (2,971,205)	2,343,338	1,621,535	1.45 (1.39–1.51)	1.40 (1.35–1.45)
12-month total indirect medical costs	1,634,510 (2,712,969)	0 (2,592,329)	886,874 (1,644,279)	0 (1,314,869)	747,635	0	1.80 (1.73–1.86)	1.65 (1.60–1.70)
HZ without complications[*]								
12-month total medical costs per patient	6,023,199 (11,672,713)	2,789,406 (4,556,667)	4,894,332 (10,737,809)	2,059,941 (3,712,020)	1,128,867	729,465	1.17 (1.16–1.19)	1.16 (1.15–1.18)
12-month total direct medical costs	4,594,379 (11,205,638)	1,394,415 (3,136,480)	3,758,663 (10,303,361)	1,008,750 (2,379,790)	835,716	385,665	1.16 (1.15–1.18)	1.16 (1.15–1.18)
12-month total indirect medical costs	1,428,819 (1,855,134)	997,474 (2,065,940)	1,135,669 (1,658,935)	670,296 (1,614,030)	293,151	327,179	1.21 (1.19–1.22)	1.20 (1.19–1.21)

Cost was adjusted 2020 Korean won using healthcare component of the Korean Consumer Price Index. The exchange rate conversion for KRW to USD based on the 2020 conversion rate from UNCTAD was 1 KRW = 0.00085 USD (UNCTAD STAT. Currency exchange rates, annual 2023 [cited 2023 Oct 19]. Available from https://unctadstat.unctad.org/datacentre/dataviewer/US.ExchangeRateCrosstab)

AID autoimmune disease, *CCI* Charlson comorbidity index, *CI* confidence interval, *HZ* herpes zoster, *IC* immunocompromised condition, *IQR* interquartile range, *PHN* postherpetic neuralgia, *SD* standard deviation, ₩ Korean Republic won

[a]Matched according to age group, sex, CCI, and prevalence period of IC/AID

[b]Differences of healthcare resource utilization between IC/AID with HZ and matched group

[c]Estimated by generalized linear model with log-gamma distribution

[d]Adjusted for age group, sex, medical institution on the index date, CCI score, common comorbidities, medical costs per patient, number of outpatient visits, number of hospitalizations, and mean length of stay per hospitalization within 1 year prior to the index date

[e]Overall HZ includes individuals diagnosed with HZ with PHN or HZ without complications among individuals with IC/AID and their matched individuals

[f]HZ with complications included patients diagnosed with both HZ and complications among patients with IC/AID and their matched individuals

[g]HZ without complications included patients diagnosed with both HZ and B02.9 or only HZ among patients with IC/AID and their matched individuals

*Complications include cutaneous, disseminated, ocular, neurologic, and other complications

different observation periods among patients with IC/AID with at least 1-year of follow-up. The incremental burden of all-cause total medical costs was observed in patients with IC/AID and HZ and incurred additional costs of 1,338,475 KRW (1138 USD) during the 12-month observation period. This increase was mainly driven by increased medical costs for outpatient visits, reflecting the high healthcare needs after HZ for patients with IC/AID. Our current study also found that the mean annual increment of total medical costs was 3,090,973 KRW (2627 USD) in patients with IC/AID and PHN compared to those without HZ. In contrast, the mean annual increment of total medical costs for patients with IC/AID and complications other than PHN compared to those without HZ was 1,316,012 KRW (1119 USD; Table 5). These findings likely indicate that the high HZ-associated medical costs and disease burden in patients with IC/AID are mainly driven by PHN, highlighting the need to pre-emptively encourage HZ immunization in patients with IC/AID to reduce the burden of HZ. Each patient with IC/AID and HZ incurred an incremental all-cause total medical cost of nearly 1,800,000 KRW (1530 USD) annually compared with each patient with IC/AID without HZ. When stratified by resource categories, the costs of medical care during the 1-year observation period were significantly higher in patients with IC/AID presenting with HZ compared to those without HZ (Table 4). These results are consistent with a previous study in which it was noted that outpatient visits were the major cost drivers in patients with HZ, and hospitalization costs had a substantial share in the overall medical cost of patients with IC/AID and PHN [32].

Limitations

When interpreting the findings of this study, one needs to consider the limitations on the use of administrative claims data. Unmeasured confounding which cannot be assessed from the medical claims database (e.g., environmental and lifestyle factors, markers of clinical severity, functional status, degree and potential risks of immunosuppression, and frailty) may affect the findings of this study.

As medical claims data are collected mainly for reimbursement purposes, rather than research, there are some inherent limitations such as incomplete, inaccurate, or missing data. Specifically, as this study relied on the ICD-10 diagnostic codes for measuring exposure, outcome, and covariate status from the procured data, there is a possibility for miscoding or misdiagnosis which would consequently lead to under- or overestimation of the true rate of variables assessed. For observational studies based on claims data involving rare or intractable diseases, such as ulcerative colitis or Crohn's disease, combining ICD codes with rare intractable disease (RID) codes (which are implemented by the NHIS to provide support for patients with RIDs in ROK) is recommended to enhance the accuracy of diagnostic data captured [33].

Information on non-reimbursed procedures and prescription medications, and on over-the-counter drugs were not captured, which may also affect the estimates presented here. Additionally, selection bias may have occurred as patients with IC/AID and HZ likely had more comorbidities compared with those without HZ, which may have increased healthcare-seeking behavior in these patients. HZ incidence in the IC/AID population may also be underestimated, as the HZ incidence related to each specific IC/AID condition was estimated; hence, patients diagnosed with two or more IC/AID conditions (who may have a higher risk of HZ diagnosis) were excluded from this study. Given the potential complexities of analyzing data with multiple IC/AID conditions due to the diverse disease characteristics for each specific condition, this study was designed to facilitate subgroup analysis specific to each IC/AID condition. The authors encourage future studies in which multiple IC/AID conditions are examined concurrently.

Finally, HIRA has a restriction on the maximum size of data extractable, and the size of data for the non-IC/AID population far exceeded the upper limit and was not available from HIRA for analysis. Data from an alternative source, NHIS-National Sample Cohort (NSC), a

longitudinal dataset which is a systemically sampled cohort of 2.2% of the entire population established by NHIS, was used to estimate the size of the non-IC/AID population in ROK, and provides useful information regarding HCRU to public health researchers and policy makers [16]. However, NHIS-NSC data was only accessible up to 31 December 2019.

CONCLUSION

In this retrospective nationwide cohort study, we observed a substantial disease and economic burden from HZ among patients with IC/AID. There is therefore a need for targeted prevention approaches for immunologically susceptible populations at increased risk of HZ who are aged above 18 years in ROK, particularly as the live-attenuated zoster vaccines are contraindicated for these patients.

Overall, our study addressed the current knowledge gap in HZ among the specific population in ROK and will inform healthcare providers of HZ burden of disease in the patient cohort for HZ awareness and prevention, including vaccination.

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Data Availability. According to Health Insurance Review and Assessment Service (HIRA)'s policy, source data cannot be shared.

Declarations

Conflict of Interest. Jing Chen and Sumitra Shantakumar: Employees of and hold shares in GSK group of companies; Ju-Young Shin, Sungho Bea, and Dong-Gun Lee: Report nothing to disclose; Byong Duk Ye: Received grants/contracts from Celltrion and Pfizer; received consulting fees from BMS, Chong Kun Dang Pharm, CJ Bioscience, Curacle, Daewoong Pharm, Dong-A ST, IQVIA, Korea Otsuka Pharm, Korea United Pharm, Medtronic, NanoEntek, ORGANOIDSCIENCES, and Samsung Bioepis; received payment/honoraria from AbbVie, Celltrion, Cornerstone Health, Curacle, Daewoong Pharm, Eisai, Ferring, IQVIA, Janssen, Pfizer, and Takeda; participated on Data Safety Monitoring Boards or Advisory Boards by AbbVie, Celltrion, Ferring, Janssen, Pfizer, Takeda, and Yuhan; Hyungwoo Kim: Employee of GSK group of companies; Won Suk Choi: Received payment/honoraria for lectures on the zoster vaccine to physicians. Iain Kaan: Previously an employee and shareholder of GSK group of companies and currently an independent researcher. The authors declare that the conflicts of interest reported are outside this submitted work, and that there are no conflicts of interest that could have influenced the design, conduct, or reporting of this research.

Ethical Approval. This study was performed in accordance with the ethical principles outlined in the Helsinki Declaration of 1964, its later amendments, and all applicable laws and regulations governing research

involving human participants. Approval for this study was obtained from the Sungkyunkwan University (SKKU) Ethics Committee (Protocol number SKKU 2021-03-008) and followed the guidelines and recommendations provided by the aforementioned ethics committee. As the databases used for this retrospective claims analysis study consisted of Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant de-identified data, informed consent for publication was not required. Confidentiality and anonymity are implied owing to the nature of this database analysis.

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