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Costs of herpes zoster complications in older adults: A cohort study of US claims database

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ABSTRACT

Background/Objectives: Herpes zoster (HZ) incidence increases with age, and the burden of HZ is expected to grow with aging of populations worldwide. We aim to determine the incremental healthcare resource utilization and associated costs of patients with common HZ-related complications other than postherpetic neuralgia (cutaneous, neurologic and ophthalmic) compared to uncomplicated HZ.

Methods: We conducted a retrospective cohort study of commercial health insurance claims covering about 40 million immunocompetent individuals aged ≥50 years at study entry from all over the US, from 2008 to 2013, with follow-up for one year after HZ onset. All-cause healthcare resource utilization and direct healthcare costs were recorded and calculated from six months before until 12 months after HZ onset. The mean costs for HZ patients with complications were compared to the mean costs for patients with uncomplicated HZ. Multivariable regression analyses estimated mean incremental costs adjusted for demographics, comorbidities, type of complication and time period.

Results: Over the five-year study period, 22,948 HZ patients (60% women, median age 62 years) who experienced at least one of the selected complications were compared to 213,232 patients (63% women, median age 61 years) with uncomplicated HZ. Overall, the mean annual incremental unadjusted costs for the patients with HZ-related complications were US$4716, ranging from US$2173 for ophthalmic to US $18,323 for neurologic complications. Most of the incremental costs associated with HZ complications were accrued during the first quarter after HZ onset. For each complication type the incremental costs increased with age up to, but not including the oldest group, aged ≥80 years.

Conclusions: Approximately 10% of immunocompetent older patients with HZ develop complications which considerably increase the economic burden of HZ. Vaccination of older adults will offset some of the burden of HZ, including costs associated with HZ-related complications.

1. Introduction

Herpes zoster (HZ) is a painful, neurocutaneous disease caused by reactivation of varicella-zoster virus (VZV), which remains latent in dorsal root or cranial nerve ganglia after a primary VZV infection [1]. VZV is endemic worldwide and almost one in three individuals in the US will develop HZ during their lifetime [2–4]. VZV may reactivate to cause HZ at any age, but the HZ risk increases substantially with age after 50 years of age, concurrently with the age-related decline in VZV-specific cell-mediated immunity [5,6]. Increasing life expectancy worldwide suggests that the burden of HZ will increase in years to come [7].

In addition to the rash and pain that characterize the acute phase of HZ, many patients experience complications, the most common of which is postherpetic neuralgia (PHN), which entails persistent pain that can last for many months. Other, less frequent complications of HZ include secondary infections of HZ rash, eye complications, and neurologic complications. Combined, these

Abbreviations: CCI, Charlson comorbidity index; HCRU, healthcare resource utilization; HZ, herpes zoster; ICD-9-CM, International Classification of Diseases 9th Revision, Clinical Modification; PHN, postherpetic neuralgia; SD, standard deviations; VZV, varicella-zoster virus.

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non-PHN complications affect approximately 10% of patients with HZ [5,8]. PHN and other HZ complications are more frequent with increasing age at HZ onset [6–8].

HZ is a vaccine-preventable disease, current recommendations from Advisory Committee on Immunization Practices suggest vaccination of adults 50 years of age and above [9]. Understanding current costs associated with the disease is important, as recommendations are evaluated for cost-effectiveness. There are few studies of the costs of HZ-related complications and only one published analysis assessed the incremental costs of HZ due to complications other than PHN compared to uncomplicated HZ [8]. That study observed substantial incremental costs of non-PHN HZ complications, but the study population consisted of HZ cases in a single county in the US, and included immunocompromised individuals. National and more contemporary information on the costs of HZ-related complications other than PHN in immunocompetent patients is needed. As previous research has focused on the incremental costs associated with PHN [10], the purpose of the present study was to assess the incidence of HZ-related complications other than PHN; to record the incremental healthcare resource utilization (HCRU) due to these complications; and to determine the associated costs compared to uncomplicated HZ in a large cohort of immunocompetent individuals aged ≥50 years.

2. Methods

2.1. Study design

This retrospective cohort study used health insurance claims data to compare immunocompetent patients with HZ and selected HZ-related complications (exclusive of PHN) to immunocompetent patients with HZ who did not develop these complications in order to estimate the incremental average HCRU and costs associated with complications.

2.2. Study setting and data source

This study reflects recent clinical practice of insured persons through the evaluation of health insurance claims covering the period from July 2008 throughout June 2013. Data were extracted from the Truven Health Analytics MarketScan Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits administrative claims databases. These sources included commercially-insured persons enrolled in managed healthcare plans throughout the US with complete medical and pharmacy claims.

2.3. Patient selection criteria

Case identification was based on International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes (see Supplementary Table S1).

Individuals included in the study were identified based on the presence of a primary or secondary diagnosis of HZ (diagnosis code 053.xx) with the date of the first observed HZ diagnosis defined as the HZ index date. Patients were further required to have had continuous health plan enrollment from at least six months before (to ensure no prior HZ diagnoses and to allow for collection of information on baseline comorbidities) until 12 months after the HZ index date, to be ≥50 years of age at the HZ index date and to not have received any vaccination against HZ. Additionally, patients could not be immunocompromised, as determined by the absence of both a diagnosis of an autoimmune disease at any point during the study period and receipt of any medication likely to compromise immune function during the six months prior to the HZ index date. Details of the conditions and medications leading to exclusion are provided in Supplementary Table S2.

Patients with an HZ-related complication were identified based on a diagnosis for an HZ-related complication recorded on or after the HZ index date (note: complications should have occurred within either 14 or 30 days of the HZ index date, depending on complication type). Complications were classified into three categories: cutaneous, neurologic, or ophthalmic. The ICD-9-CM codes used for identification of complications and the time periods surveyed are listed in Supplementary Table S1, based on previously published literature [11]. Patients with ≥2 complications were included in each category for which they qualified.

2.4. Study outcomes

The proportion of HZ patients with HZ-related complications was estimated, overall and stratified by age groups. Demographics (i.e., age, gender, geographic location, health plan type, and payer type) were recorded at each patient's HZ index date. Clinical characteristics including the Charlson Comorbidity Index (CCI) score were assessed for the six-month period preceding the HZ index date. The CCI score includes 20 categories of comorbidities as defined by ICD-9-CM diagnosis and procedure codes, with associated weights corresponding to the severity of the comorbid condition of interest [12,13].

All-cause HCRU (i.e., regardless of diagnoses list on the claim and not limited to claims with an HZ diagnosis) and costs were calculated for each individual from the HZ index date until one year after and then summed and averaged over all the individuals in the respective cohorts. Healthcare resources were categorized as hospital inpatient stays, emergency department visits, hospital outpatient visits, physician office visits, other outpatient or ancillary care, and pharmacy claims. For each type of resource used, the number of patients with ≥1 claim(s) for this resource was reported along with the total number of claims and the average costs per patient. For inpatient hospital stays, the number of separate admissions and the average length of stay were determined.

The incremental costs of HZ complications were calculated by subtracting the costs for the uncomplicated HZ cohort from those of the HZ cohort with complications. Similar calculations were done to estimate the average incremental costs for the three types of complications separately.

2.5. Data analysis

Study outcomes were analyzed descriptively through tabular or graphical display of means, medians, ranges and standard deviations (SD) for continuous variables and frequency distributions for categorical variables. Costs included patient co-payments and health-plan payments. The cost data for each year were adjusted to 2013 US$ values by the medical care component of the US Consumer Price Index.

Average total HCRU and costs were compared using univariate tests (i.e., Student's *t*-test for continuous variables like costs and a chi-squared test for categorical variables like having been admitted in hospital or not). These comparisons were performed across the cohorts overall and for each type of complication and age group.

Multivariable regression models were estimated to derive adjusted incremental costs associated with HZ complications in the period following the HZ index date. All models controlled for patient demographics (i.e., age, sex, geographic region, health plan type, payer type), total healthcare costs in the six months preceding the HZ index date, clinical characteristics including comorbidi-

ties, presence of a PHN diagnosis, type of complication, and time period. Additionally, interaction terms were included for the cohort and period to account for the effect of changes in costs over time. We used generalized estimating equations with a log-link for the mean and a gamma distribution for the residuals to resolve the issue of skewed distributions which are common for healthcare cost data [14] (for full model details see Supplementary Materials).

A recycled predictions approach was used to assess the differences in costs with and without HZ-related complications by predicting the costs for all patients according to their overall HZ

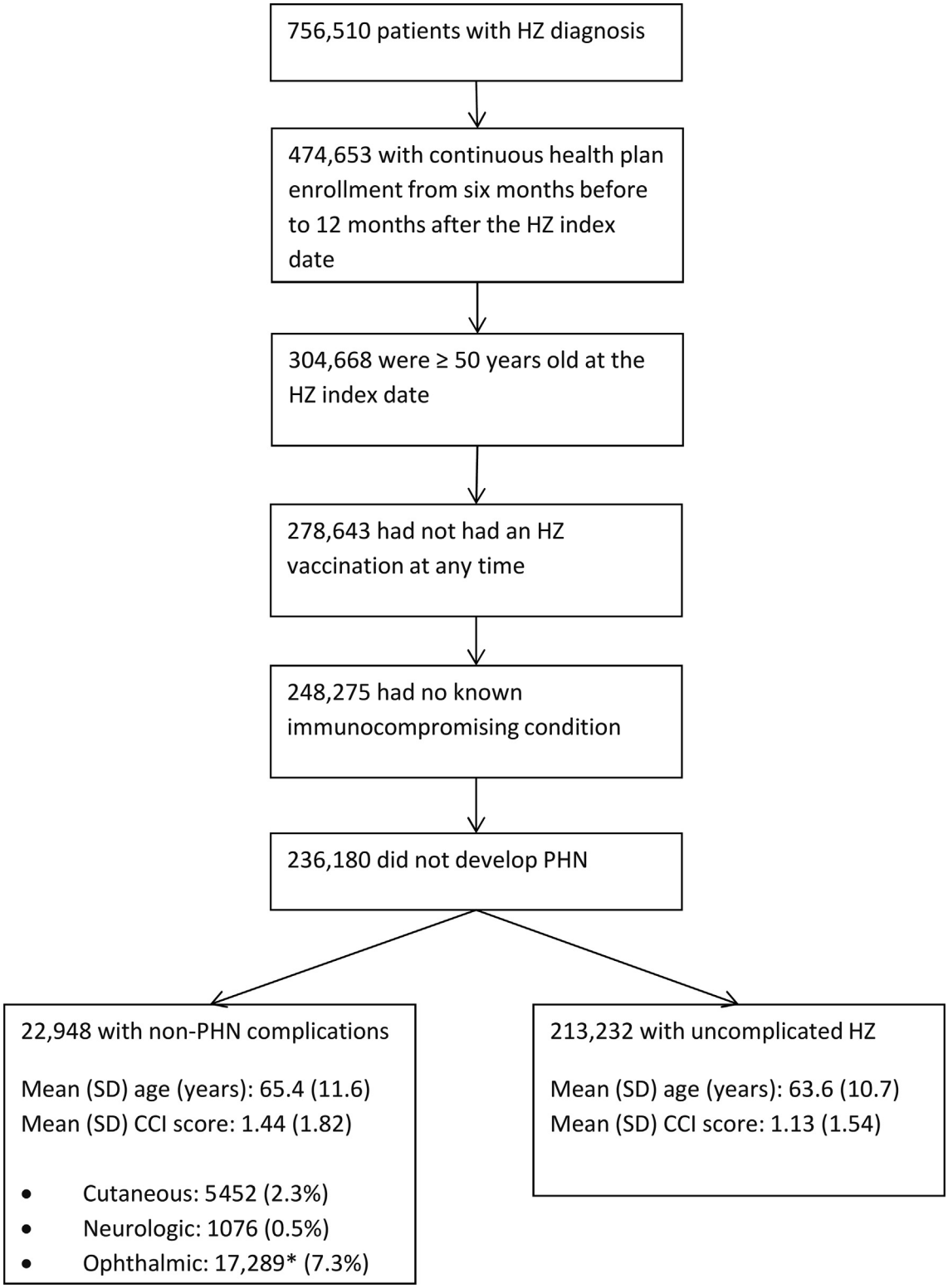


Fig. 1. Selection of the study cohort. HZ: herpes zoster; PHN: postherpetic neuralgia; SD: standard deviation; CCI: Charlson comorbidity index; *: With the broad definition of ophthalmic complications (including eyelid dermatitis).

complication status (i.e., no complication or any complication) and separately for each complication type versus no complication, using each patient's own values [15]. Patients' data were input back into the estimated regression model twice, first setting the complication variable equal to 1 for all patients (regardless of their actual complication status); in the second iteration, the complication variable was set to 0 for all patients (regardless of their actual complication status). The mean predicted value for each iteration was reported and adjusted incremental healthcare costs were reported as the adjusted mean costs when the complication variable was equal to 1 minus the adjusted mean costs when the complication variable was equal to 0. Results were reported overall and stratified by age group.

2.6. Post-hoc sensitivity analyses

In a post-hoc sensitivity analysis, the regression model was rerun with an alternative definition of ophthalmic complications. The broad definition used in the base analysis included dermatitis of the eyelid, which is expected for HZ and was therefore excluded from the narrow definition of ophthalmic complications, which included disorders specifically related to HZ (Supplementary Table S1).

3. Results

3.1. Study cohort

A total of 756,510 patients with an HZ diagnosis were identified over the study period. Among these, 236,180 met all inclusion criteria and of these, 22,948 (9.7%) had ≥1 HZ complications and 213,232 had uncomplicated HZ (Fig. 1). Of note, 35% of HZ cases occurred in subjects under 50 years of age. The most frequent complication was ophthalmic (7.3%), followed by cutaneous (2.3%) and neurologic (0.5%).

The mean age and gender distribution were similar in both cohorts, whereas patients with HZ complications had a mean CCI score of 1.44 versus 1.13 for patients with uncomplicated HZ (Fig. 1, Table 1). The proportions of patients with selected comorbidities are presented in Table 1.

The proportion of patients with any non-PHN complication increased with age, from 8.7% in patients aged 50–59 years to 13.3% in patients aged ≥80 years. The proportion of patients with neurologic complications was twice as high in patients aged ≥80 years as in patients aged 50–59, whereas for both cutaneous and ophthalmic complications the relative increase between these age groups was approximately 50% (Table 2).

Table 1
Demographics and comorbidity scores.

Category	Without HZ complication N = 213,232	With HZ complication N = 22,948	Type of complication		
			Cutaneous N = 5452	Neurologic N = 1076	Ophthalmic* N = 17,289
Patient numbers by age group, (N, %)					
50–59	95,040 (44.6)	9051 (39.4)	2260 (41.5)	419 (38.9)	6654 (38.5)
60–64	47,435 (22.3)	4636 (20.2)	1048 (19.2)	194 (18.0)	3541 (20.5)
65–69	15,320 (7.2)	1640 (7.2)	324 (5.9)	73 (6.8)	1311 (7.6)
70–79	31,349 (14.7)	3932 (17.1)	835 (15.3)	183 (17.0)	3087 (17.9)
≥ 80	24,088 (11.3)	3689 (16.1)	985 (18.1)	207 (19.2)	2696 (15.6)
Mean age in years (SD)	63.6 (10.7)	65.4 (11.6)	65.5 (12.3)	66.2 (12.1)	65.5 (11.4)
Median age in years (min–max)	61 (50–107)	62 (50–102)	62 (50–102)	62 (50–100)	62 (50–102)
Gender (column %)					
Male	79,023 (37.1)	9259 (40.4)	2266 (41.6)	415 (38.6)	6975 (40.3)
Female	134,209 (62.9)	13,689 (59.7)	3186 (58.4)	661 (61.4)	10,314 (59.7)
Charlson comorbidity index score					
Mean (SD)	1.13 (1.54)	1.44 (1.82)	1.98 (2.16)	1.99 (2.31)	1.26 (1.63)
Median (min, max)	1 (0–19)	1 (0–17)	1 (0–15)	1 (0–14)	1 (0–17)
Payer type (column %)					
Commercial	144,157 (67.6)	13,841 (60.3)	3353 (61.5)	617 (57.3)	10,305 (59.6)
Medicare	69,075 (32.4)	9107 (39.7)	2099 (38.5)	459 (42.7)	6984 (40.4)
Proportions with selected comorbidities (%)					
Heart failure	3.2	4.2	6.0	6.5	3.6
Myocar infarc	1.1	1.5	2.1	2.8	1.2
Perif vasc dis	3.7	5.0	7.1	7.4	4.3
Cerebrovasc	3.8	5.6	6.0	20.2	4.7
Dementia	0.7	0.8	1.2	1.9	0.6
COPD	8.7	10.4	12.8	12.8	9.6
Connec tissue	1.5	1.9	2.0		1.9
Ulcer	0.4	0.5	0.8	0.7	0.4
Diabetes	14.3	16.6	21.2	20.6	15.0
Depression	5.2	5.4	7.0	8.0	4.8
Warfarin use	2.8	3.7	4.3	4.3	3.5
Hypertension	33.2	36.4	41.2	44.6	34.7
Hemiplegia	0.2	0.6	0.6	5.6	0.3
Renal, mod/sev	2.5	3.4	4.3	5.9	3.0
Diab, severe	2.7	3.6	5.0	4.7	3.2
Any tumor	6.6	7.7	8.3	7.3	7.6
Skin ulcers/cell	4.2	10.0	23.5	8.6	6.4
Liver, mild	1.7	1.7	2.1	2.4	1.5
Liver, mod/sev	0.1	0.2	0.3	0.2	0.1

HZ: herpes zoster; SD: standard deviation.
* Broad definition of ophthalmic complications. Myocar infarc: myocardial infarction; Perif vasc dis: peripheral vascular disease; Cerebrovasc: cerebrovascular disease; Connec tissue : Connective tissue disease; COPD: Chronic obstructive pulmonary disease; mod/sev: moderate/severe; Diab: diabetes (end organ damage); cell: cellulitis.

Table 2
Proportion of patients with non-PHN HZ-related complications by age group.

Age group (years)	Cutaneous (%)	Neurologic (%)	Ophthalmic* (%)	Any (%)
50–59	2.2	0.4	6.4	8.7
60–64	2.0	0.4	6.8	8.9
65–69	1.9	0.4	7.7	9.7
70–79	2.4	0.5	8.8	11.1
≥80	3.5	0.8	9.7	13.3
Overall	2.3	0.5	7.3	9.7

HZ: herpes zoster.
* With the broad definition of ophthalmic complications.

3.2. Resource utilization

The overall average use of all categories of healthcare resources during the year following the HZ index date was significantly greater in HZ patients with complications than in those with uncomplicated HZ (Table 3). The largest differences were observed for physician office claims, outpatient or ancillary care claims, prescription claims and outpatient hospital visit claims. The incremental burden of HZ-related complications increased with age for inpatient admission and other outpatient or ancillary care claims, whereas there was no age-related pattern for other types of HCRU.

Hospital admissions were more frequent for HZ patients suffering from cutaneous or neurological complications (20.7% and 30.3%, respectively, had at least one visit to a hospital). HZ patients with cutaneous, neurological and ophthalmic complications had significantly more healthcare claims (29, 48 and 10 respectively) compared to HZ patients without any complication (Table 3).

3.3. Costs

3.3.1. Unadjusted costs

Patients with cutaneous and neurologic complications had higher unadjusted costs than patients with uncomplicated HZ during the six months preceding the HZ index date, respectively 1.7 and 2.7 times higher (Supplementary Figure S1). These differences reflect the higher burden of comorbidities for the patients with these complications, as both groups had a mean CCI score of almost 2 compared to the mean CCI score of 1.13 for patients with uncomplicated HZ (Table 1). Patients with ophthalmic complications also had a higher mean CCI score and higher costs preceding the HZ index date but the differences were much smaller.

Table 3
Mean unadjusted incremental HCRU for patients per HZ complication compared to patients with uncomplicated HZ during the first year after HZ index date.

	Complication type	50–59 Y	60–64 Y	65–69 Y	70–79 Y	≥80 Y	Overall
Inpatient services	Any	0.07***	0.09***	0.11***	0.13***	0.18***	0.12***
	Cutaneous	0.20***	0.26***	0.41***	0.34***	0.46***	0.31***
	Neurological	0.37***	0.34***	0.52**	0.66***	0.58***	0.49***
	Ophthalmic#	0.01	0.04*	0.03	0.06**	0.07**	0.05***
ED visits	Any	0.19***	0.33***	0.27*	0.25***	0.19+	0.28***
	Cutaneous	0.56***	0.77***	1.08*	0.53**	0.60*	0.69***
	Neurological	1.02***	1.37**	1.62	2.06***	1.63*	1.49***
	Ophthalmic#	0.05	0.19*	0.06	0.09	−0.10	0.10*
Outpatient hospital visits	Any	2.05***	2.99***	1.79+	4.55***	0.79	2.82***
	Cutaneous	5.37***	6.07***	7.83***	8.90***	4.08**	6.32***
	Neurological	9.15***	18.61***	28.62*	18.36***	11.31**	14.68***
	Ophthalmic#	0.56	1.13	−0.84	2.80+	−0.85	1.15**
Physician office visits	Any	4.33***	4.21***	6.30***	5.57***	4.21***	4.99***
	Cutaneous	6.35***	6.10***	8.96**	7.20***	3.43*	6.39***
	Neurological	8.79***	13.84**	13.20+	10.11*	−1.50	8.72***
	Ophthalmic#	3.61***	3.42***	5.26***	5.00***	4.93***	4.53***
Pharmacy	Any	2.23***	2.74***	1.67*	3.11***	2.74***	3.17***
	Cutaneous	4.31***	5.42***	4.74*	4.54**	4.24**	5.23***
	Neurological	4.67**	4.14	2.13	8.02*	5.33*	6.01***
	Ophthalmic#	1.47***	1.99**	0.99	2.56***	2.52**	2.57***
Other medical encounters	Any	1.36***	2.76***	3.12*	4.47***	7.13***	3.95***
	Cutaneous	4.03***	7.50***	11.65*	13.32***	18.84***	10.08***
	Neurological	7.32*	13.28**	6.33+	20.95***	34.54***	16.96***
	Ophthalmic#	0.12	0.84	0.87	1.51	1.10	1.43***
Total healthcare utilization	Any	10.23***	13.12***	13.25***	18.08***	15.24***	15.34***
	Cutaneous	20.82***	26.10***	34.66***	34.83***	31.65***	29.03***
	Neurological	31.32***	51.57***	52.42*	60.16***	51.90***	48.36***
	Ophthalmic#	5.83***	7.60***	6.35*	12.01***	7.68**	9.84***

For example, patients with a HZ complication had on average 4.99 more office visit claims compared with patients without a HZ complication.
*** p-value < 0.0001.
** p-value < 0.001.
* p-value < 0.01.
+ p-value < 0.05.
# With the broad definition of ophthalmic complications (including eyelid dermatitis). ED: emergency department; HCRU: healthcare resource utilization; Y: years; HZ: herpes zoster.

The mean incremental unadjusted costs for patients with any HZ complication compared to patients with uncomplicated HZ during the first year following the HZ index date tended to increase with age and ranged from US$2925 for patients aged 50–59 years to US$5923 for patients aged 70–79 years, then decreased for patients aged ≥80 years (Table 4). Overall, the mean incremental costs ranged from US$2173 for patients with ophthalmic conditions, to US$11,081 for patients with cutaneous complications, and US$18,323 for patients with neurologic complications (Table 4). Fig. 2 and Supplementary Table S3 show the composition of the mean incremental costs by type of complication. For cutaneous and neurologic complications, almost half of the mean incremental costs were associated with inpatient hospital stays, whereas the incremental costs for ophthalmic complications were more evenly distributed across the various types of medical resources.

3.3.2. Adjusted costs

During the first year after the HZ index date, patients with any HZ complication accrued mean adjusted costs of US$13,839 compared to US$11,595 for the patients with uncomplicated HZ. About one-third of this difference was accrued during the first month after the HZ index date and about half during the first quarter after the HZ index date (Supplementary Figure S2).

The highest mean incremental costs for all age groups combined were observed for patients with neurologic complications (US$10,918) and the lowest for those with ophthalmic complications (US$534) (Supplementary Figure S2, panels B-D). For patients with neurologic complications, 76% of the incremental costs were accrued during the first month after the HZ index date (Supplementary Figure S2 panel C), whereas the distribution of incremental costs over time in the two other complication categories were similar to the overall cohort of patients with HZ complications (Supplementary Figure S2, panels B and D).

The mean incremental costs for patients with any HZ complication increased monotonically with age and this age-related pattern was observed for each of the complication categories separately (Table 5). By contrast, for the unadjusted costs, the incremental costs increased with advancing age up to the group aged 70–79 years and then decreased for HZ patients aged ≥80 years (Table 4).

In the post-hoc analysis with a narrower definition of ophthalmic complications (excluding eyelid dermatitis), the number of patients with ophthalmic complications was reduced by more than 60% to 6724 and the mean incremental adjusted costs for this category increased from US$534 to US$785 during the first year after the HZ index date (Supplementary Table S4).

4. Discussion

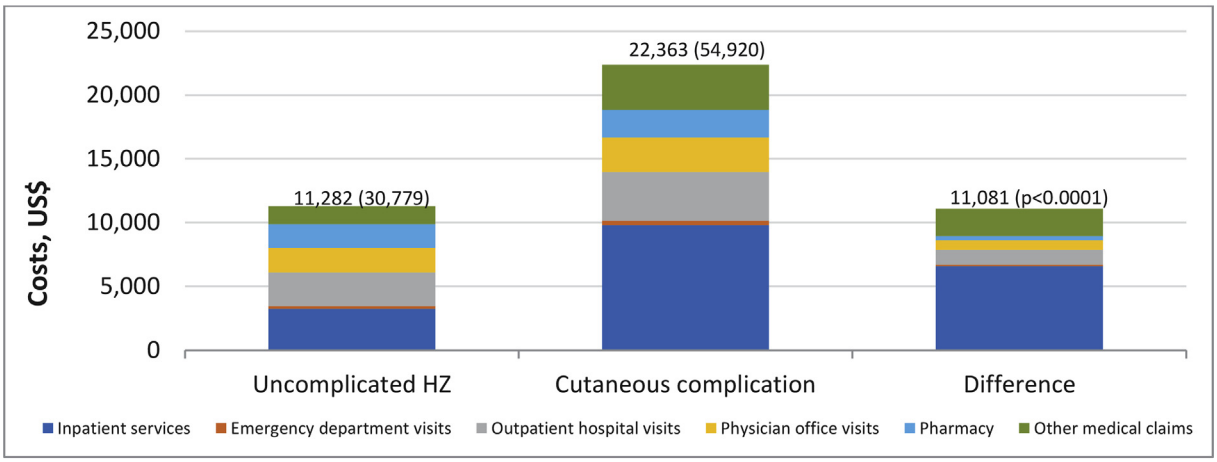
Almost 10% of the HZ patients experienced ≥1 of the non-PHN complications evaluated in this analysis, which documents a greater use of healthcare resources and higher associated costs in immunocompetent patients with HZ who developed non-PHN complications compared to patients with uncomplicated HZ

Table 4
Mean unadjusted incremental costs (in US$) for patients with any HZ complication compared to patients with uncomplicated HZ during the first year after HZ index date.

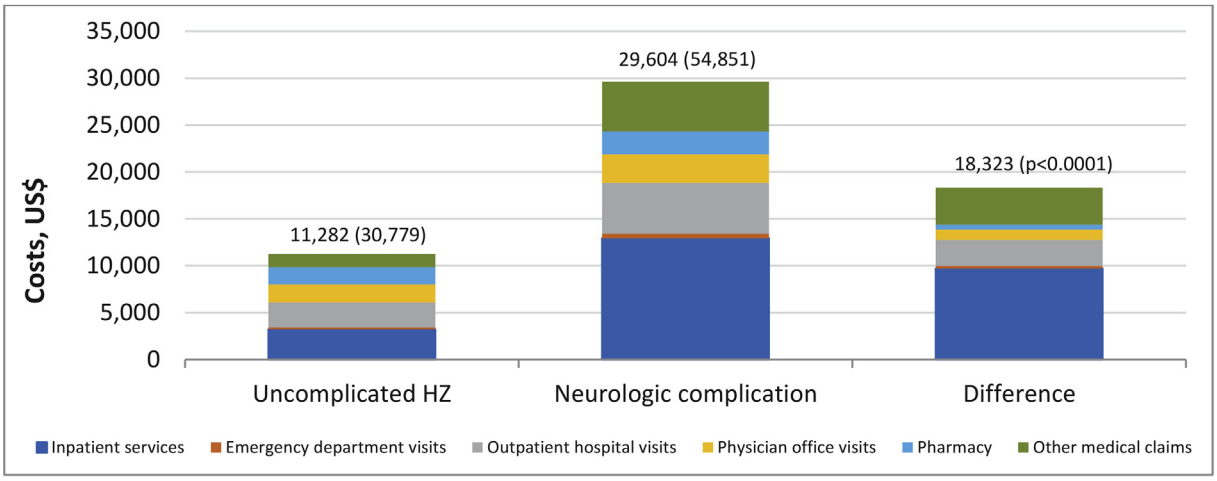
	Complication type	50–59 Y	60–64 Y	65–69 Y	70–79 Y	≥80 Y	Overall
Inpatient services	Any	1422***	1640***	2530***	3289***	2697***	2345***
	Cutaneous	4336***	5505***	10,342***	9010**	7900***	6573***
	Neurological	8303***	10,018**	8654*	11,833**	8583***	9686***
	Ophthalmic#	102	146	480	1501+	673	758**
ED visits	Any	43***	78***	64*	64***	64*	66***
	Cutaneous	116***	136**	253*	89**	82+	128***
	Neurological	235*	251*	466+	339**	294*	294***
	Ophthalmic#	12	57*	8	45+	39	37***
Outpatient hospital visits	Any	456***	646**	649	875*	196	589***
	Cutaneous	948***	1494*	2312+	1622	401	1178***
	Neurological	1273*	5425*	4550+	5144	304	2779***
	Ophthalmic#	240	106	108	410	210	285*
Physician office visits	Any	488***	524***	722***	548***	353***	553***
	Cutaneous	639***	1078*	1000*	753**	303	750***
	Neurological	1149**	1284**	3945	691*	−185	1099***
	Ophthalmic#	403***	388**	461**	484***	409***	475***
Pharmacy	Any	329***	314***	254+	258**	112	329***
	Cutaneous	319**	317+	377	278	131	327***
	Neurological	954*	651	65	182	−218	554**
	Ophthalmic#	298***	294**	242	256*	150+	324***
Other medical encounters	Any	187*	361*	280	889***	2094***	835***
	Cutaneous	851***	1168**	1297*	2524***	4832***	2124***
	Neurological	799*	1983**	429	4605***	11,209**	3910***
	Ophthalmic#	−78+	27	13	299	559	294*
Total healthcare utilization	Any	2925***	3564***	4499***	5923***	5517***	4716***
	Cutaneous	7209***	9697***	15,580***	14,277***	13,650***	11,081***
	Neurological	12,712***	19,613***	18,110*	22,793***	19,986***	18,323***
	Ophthalmic#	977+	1018	1311	2995**	2039+	2173***

ED: emergency department; p-value: significance of difference between the compared groups; Y: years; HZ: herpes zoster.
For example, patients with a HZ complication had on average $553 costs incurred more for office visits compared with patients without a HZ complication.
*** p-value < 0.0001.
** p-value < 0.001.
* p-value < 0.01.
+ p-value < 0.05.
# With the broad definition of ophthalmic complications (including eyelid dermatitis).

Cutaneous



Neurologic



Ophthalmic*

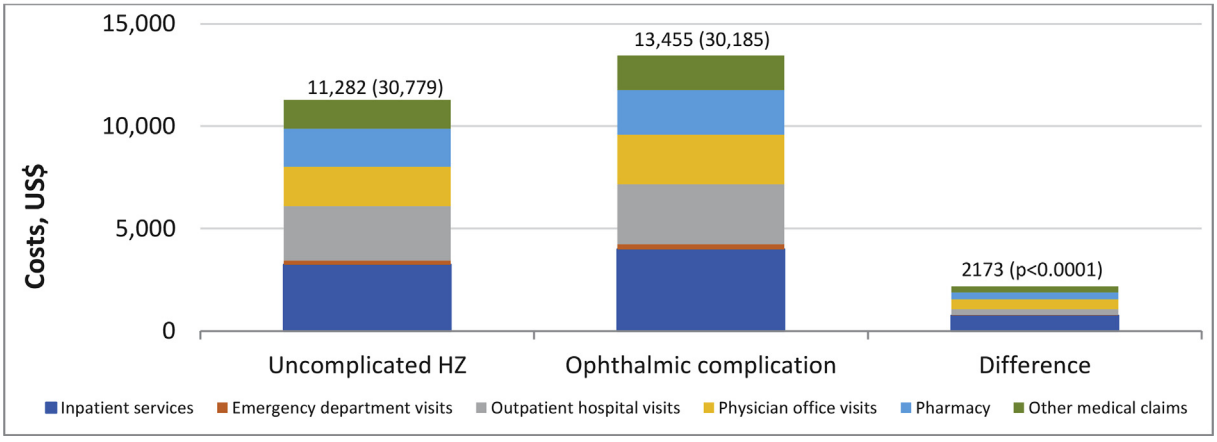


Fig. 2. Mean unadjusted healthcare costs during the first year after the HZ index date. HZ: herpes zoster; *: With the broad definition of ophthalmic complications (including eyelid dermatitis); SD: standard deviation.

Fig. 3. Depending on the complication, between half and two-thirds of the incremental adjusted annual costs associated with HZ complications were accrued during the first quarter after the HZ index date. The incremental HCRU costs varied by complication category, with more costs associated with hospital admissions within cutaneous and neurologic complications and more costs

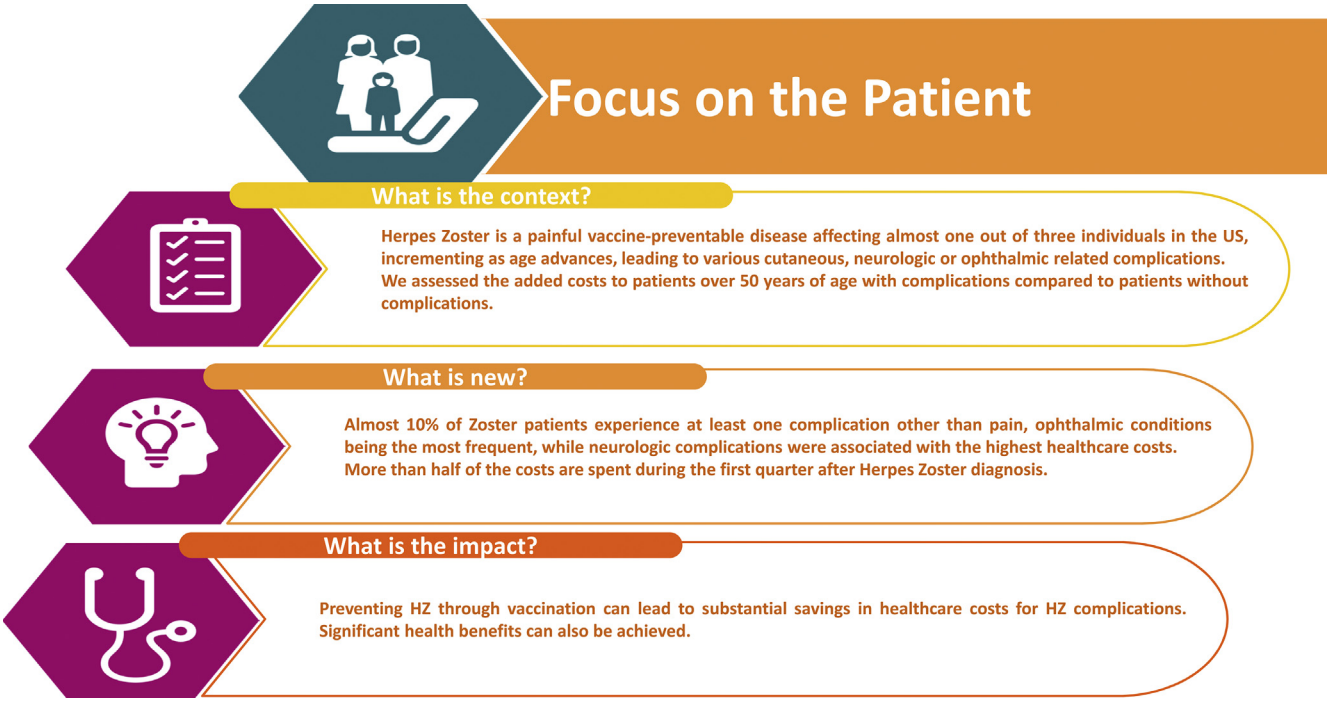


Fig. 3. Focus on the patient section.

Table 5
Mean adjusted healthcare costs (in US$) for HZ patients with complications compared to patients with uncomplicated HZ. Mean (SD).

Complication type	50–59 Y	60–64 Y	65–69 Y	70–79 Y	≥ 80 Y	Overall
Uncomplicated*	8111 (6564)	10,286 (8505)	11,610 (9682)	15,960 (12,620)	21,547 (16,488)	11,595 (10,847)
Any complication	9681 (7835)	12,278 (10,151)	13,858 (11,556)	19,050 (15,063)	25,719 (19,680)	13,839 (12,947)
Difference *(p value)*	***1570*** *(p < .0001)*	***1991*** *(p < .0001)*	***2248*** *(p < .0001)*	***3090*** *(p < .0001)*	***4171*** *(p < .0001)*	***2245*** *(p < .0001)*
Uncomplicated	8103 (6153)	10,274 (8433)	11,591 (9598)	15,952 (12,515)	21,434 (16,276)	11,573 (10,748)
Cutaneous	11,955 (9609)	15,157 (12,441)	17,100 (14,160)	23,534 (18,463)	31,621 (24,012)	17,073 (15,856)
Difference *(p value)*	***3851*** *(p < .0001)*	***4883*** *(p < .0001)*	***5509*** *(p < .0001)*	***7582*** *(p < .0001)*	***10,187*** *(p < .0001)*	***5500*** *(p < .0001)*
Neurologic	15,748 (12,658)	19,966 (16,389)	22,526 (18,652)	31,002 (24,321)	41,655 (31,631)	22,490 (20,888)
Difference *(p value)*	***7645*** *(p < .0001)*	***9692*** *(p < .0001)*	***10,935*** *(p < .0001)*	***15,050*** *(p < .0001)*	***20,221*** *(p < .0001)*	***10,918*** *(p < .0001)*
Ophthalmic#	8477 (6814)	10,748 (8822)	12,126 (10,041)	16,688 (13,092)	22,423 (17,027)	12,107 (11,244)
Difference *(p value)*	***374*** *(p < .0001)*	***474*** *(p < .0001)*	***535*** *(p < .0001)*	***736*** *(p < .0001)*	***989*** *(p < .0001)*	***534*** *(p < .0001)*

SD: standard deviation.
* Based on the separate regression model for any complication vs. no complications.
# Broad definition of ophthalmic complications.

associated with physician-office-visit along with outpatient-visit claims within ophthalmic complications.

There are few studies of the economic burden of HZ-related complications other than PHN [16] and only one with an extensive economic assessment of specific non-PHN HZ complications including ocular, skin, and neurologic complications [8]. That study, by Yawn et al., which included both immunocompetent and immunocompromised patients, found mean total healthcare costs over the three weeks before and the first quarter after HZ onset amounting to US$3850, US$4928, and US$2810 for skin, neurologic, and ocular complications, respectively. The corresponding first-quarter mean total unadjusted costs by complication in our study were US$8949, US$15,672 and US$4337, respectively. The ranking of costs by type of complication and the pattern of incremental HCRU was the same in both studies.

Part of the differences in the costs calculated in the two studies may be explained by increases in unit costs, since Yawn et al. used 2006 data whereas all the annual costs associated with claims and patient co-payment data in our study across the seven years were inflated to reflect 2013 prices. Furthermore, patients in our study were all ≥50 years old, whereas one-third of the patients in the Yawn study were <50 years old. The major reason, however, is likely to be that we included all-cause healthcare costs whereas Yawn and colleagues included only costs considered to be directly attributable to HZ and its complications [8].

The mean incremental unadjusted costs associated with any complication increased with age until the oldest patients aged ≥80 years, for whom unadjusted costs fell somewhat relative to those in the age group 70–79 years. A similar trend was found by Yawn et al., who defined the oldest group as patients aged ≥70 years [8]. Partly, this pattern is explained by the fact that for the patients with uncomplicated HZ the mean annual total costs were 25% higher for the oldest compared to patients aged 70–79 years, whereas for the patients with complications the relative

increase in mean total annual costs from the next-oldest to the oldest patients ranged from 3% to 16%. We speculate that patients with HZ complications give less priority to other, concurrent health problems or receive attention for these as part of the care received for the HZ complications without additional claims being generated for the concomitant care.

Higher CCI correlated with higher likelihood of HZ. HZ patients with cutaneous and neurologic complications had markedly higher mean co-morbidity scores than the patients with uncomplicated HZ, and also incurred higher costs during the six-month period preceding the HZ index date than patients with uncomplicated HZ. Thus, higher comorbidities may be indicative of having a higher likelihood of HZ complications. Notably, individuals with certain pre-existing disorders like cerebrovascular disorders or skin ulcers/cellulitis are at higher risk of developing neurologic and cutaneous complications when experiencing an episode of HZ, or more likely to receive additional medical care. This is not unexpected as several previous studies have found some comorbidities to be associated with higher risks of HZ or complications. Suaya et al [17] found that diabetes patients had increased risks of HZ and complications. Similarly, in a meta-analysis, Kawai and Yawn reported that autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematous, but also asthma, diabetes and chronic obstructive pulmonary disease were associated with higher risks of HZ [18].

As for any analysis using administrative claims data, a limitation is that the administrative billing records may be subject to miscoding, and no clinical data or electronic health records were available to confirm diagnoses and clinical events. Patients with HZ and related complications, who did not seek medical care, were not included in the analysis, so the economic burden per HZ episode from the healthcare payer perspective may be overestimated, although it is unlikely that an HZ case would not be seen by a doctor. Costs may also be underestimated, however, because healthcare services or procedures and medications paid entirely out of pocket by the patients or covered by other supplemental health insurance were not included. In addition, the databases do not include any treatment not covered by insurance, such as over-the-counter medications or visits to non-conventional healthcare providers.

Finally, these results may not be extrapolated to a more general US or non-US population aged $\geq$50 years even though the data are representative of the commercially insured population. However, the Truven MarketScan database is one of the largest and most representative datasets in the US and these data enhance our understanding of the burden of HZ disease beyond the smaller cohorts included in previous studies.

5. Conclusion

Most of the mean incremental costs of HZ-related complications compared to uncomplicated HZ were accrued during the first quarter after the HZ index date, but continued to accrue throughout the whole follow-up year. Preventing HZ through achieving a high vaccination coverage of older adults with effective vaccines will lead to substantial savings in healthcare costs for HZ complications that extend beyond the costs of caring for uncomplicated HZ cases. These cost offsets should be taken into account when considering vaccination strategies against HZ and the costs involved.

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Conflicts of interest

DR and BP are employees of the GSK group of companies and report ownership of stock options/restricted hold shares from the GSK group of companies. SY was an employee of the GSK group of companies at the time of the study and is currently employed by CSL Behring. BP reports personal fees and non-financial support from American Pharmacists Association, personal fees and non-financial support from Pennsylvania Pharmacists Association. JLM and SDC are employed by RTI Health Solutions, report fees for services to their institution from the GSK group of companies during the conduct of the study. MJL received fees from Merck Sharpe & Dohme and the GSK group of companies for advisory boards; he received research support from these companies.

Contributorship

ML, SC, DR, SY, JM contributed to the conception and design of the study, ML, SC, SY, JM contributed to acquisition of data. All authors contributed to the analysis and interpretation of data and revised the article critically for important intellectual content. All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.079.

References

[1] Johnson RW, Dworkin RH. Treatment of herpes zoster and postherpetic neuralgia. BMJ 2003;326(7392):748–50.
[2] Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med 2005;20(8):748–53.
[3] Centers for Disease Control and Prevention (CDC). CDC's advisory committee recommends "shingles" vaccination (online). October 26, 2006. Available at <https://www.cdc.gov/media/pressrel/r061026.htm> [Accessed June 12, 2017].
[4] Pinchinat S, Cebrián-Cuenca AM, Bricout H, et al. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis 2013;13:170.
[5] Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc 2007;82(11):1341–9.
[6] Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 2014;4:e004833. doi: 10.1136/bmjopen-2014-004833. PMID: 24916088; PMCID: PMC4067812.
[7] Varghese L, Standaert B, Olivieri A, et al. The temporal impact of aging on the burden of herpes zoster. BMC Geriatr 2017;17(1):30.
[8] Yawn BP, Itzler RF, Wollan PC, et al. Health care utilization and cost burden of herpes zoster in a community population. Mayo Clin Proc 2009;84(9):787–94.
[9] Advisory Committee on Immunization Practices. Zoster (Shingles) ACIP Vaccine Recommendations; 2018. Available from: <https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/shingles.html> [Last accessed: September 10, 2018].
[10] Meyers JL, Madhwani S, Rausch D, et al. Analysis of real-world health care costs among immunocompetent patients aged 50 years or older with herpes zoster in the United States. Human Vacc Immunother 2017;13(8):1861–72.
[11] Yawn BP, Wollan P, St Sauver J. Comparing shingles incidence and complication rates from medical record review and administrative database estimates: how close are they? Am J Epidemiol. 2011;174(9):1054–61.

[12] Charlson ME, Charlson RE, Peterson JC, et al. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol. 2008;61(12):1234–40.
[13] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45(6):613–9.
[14] Wedderburn RWM. Quasi-likelihood functions, generalized linear models, and the Gauss-Newton method. Biometrika. 1974;61:439–47.
[15] Basu A, Rathouz PJ. Estimating marginal and incremental effects on health outcomes using flexible link and variance function models. Biostatistics 2005;6(1):93–109.
[16] Panatto D, Bragazzi NL, Rizzitelli E, et al. Evaluation of the economic burden of herpes zoster (HZ) infection. A systematic literature review. Hum Vacc Immunother 2015;11(1):245–62.
[17] Suaya JA, Chen SY, Li Q, Burstin SJ, Levin MJ. Incidence of herpes zoster and persistent post-zoster pain in adults with or without diabetes in the United States. Open Forum Infect Dis 2014;1(2):ofu049.
[18] Kawai K, Yawn BP. Risk factors for herpes zoster: a systematic review and meta-analysis. Mayo Clin Proc 2017;92(12):1806–21.