












Burden of Herpes Zoster Among Patients with Psoriatic Arthritis in the United States

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Purpose: Patients with psoriasis (PsO) and psoriatic arthritis (PsA) are at increased risk of herpes zoster (HZ), but healthcare resource use (HRU) and costs relating to HZ in adults with PsA are unknown. We aimed to estimate the incidence of HZ among adults with PsA vs without psoriatic disease and the additional HRU and costs among patients with PsA with vs without HZ.

Patients and Methods: This retrospective, longitudinal, cohort study estimated HZ incidence in PsA+ vs PsO-/PsA- cohorts and HRU and medical/pharmacy costs among PsA+/HZ+ vs PsA+/HZ- cohorts comprised of adults from Optum's de-identified Clinformatics Data Mart Database during 2015–2020. For the HRU/cost analyses, index was the date of first HZ diagnosis (PsA+/HZ+ cohort) or was randomly assigned (PsA+/HZ- cohort). Generalized linear models were used for adjusted comparisons between cohorts.

Results: HZ incidence was higher in the PsA+ (n = 57,126) vs PsO-/PsA- (n = 23,837,237) cohort (14.85 vs 7.67 per 1000 person-years; adjusted incidence rate ratio [aIRR]: 1.23; 95% confidence interval [CI]: 1.16–1.30). Numbers of outpatient visits, emergency department visits, and inpatient admissions were significantly higher in the PsA+/HZ+ (n = 1045) vs PsA+/HZ- (n = 36,091) cohorts during the first month after HZ diagnosis (outpatient: aIRR: 1.74; 95% CI: 1.63–1.86; emergency department: 3.14; 95% CI: 2.46–4.02; inpatient: aIRR: 2.61; 95% CI: 1.89–3.61). Mean all-cause per-patient costs were significantly higher in the PsA+/HZ+ vs PsA+/HZ- cohorts during the first month after index (\$6493 vs \$4521; adjusted cost difference: \$2012; 95% CI: \$1204–\$3007). HRU and costs were numerically higher in the PsA+/HZ+ cohort during the first 3 and 12 months.

Conclusion: These findings, which provide evidence on the increased incidence and HRU and economic burden associated with HZ among adults with PsA, could be used to inform clinical practice and decision-making.

Plain Language Summary:

Why was the study done?

- Psoriatic arthritis affects the joints of around 20% of patients with the skin condition, psoriasis.
- Patients with psoriatic arthritis are at increased risk of shingles, which can cause a painful skin rash and complications.
- This study aimed to provide information on how many patients with psoriatic arthritis get shingles and the healthcare use and costs of caring for patients with psoriatic arthritis and shingles.

What did the researchers do and find?

- Using data from a large US health plan database, we estimated that for every 1000 patients with psoriatic arthritis observed for 1 year, 15 will develop shingles.
- Patients with psoriatic arthritis were 23% more likely to develop shingles than people without psoriatic disease.
- Patients with psoriatic arthritis and shingles had 2–3 times as many healthcare visits in the month after a shingles diagnosis as patients with psoriatic arthritis but no shingles.
- This resulted in an average additional cost of approximately \$2000 per patient.

What do these results mean?

- Psoriatic arthritis increases the risk of shingles.
- The costs associated with shingles in patients with psoriatic arthritis are substantial.
- Measures to prevent shingles in this population could be beneficial.

Keywords: claims database, costs, healthcare resource use, incidence, psoriatic arthritis, United States

Graphical Abstract

Background



Patients with psoriatic arthritis (PsA) are at increased risk of herpes zoster (HZ) due to underlying disease and due to use of medications targeting the immune system.

Methods

The study objectives were:

1. Estimate the incidence of HZ among adult patients with PsA vs. without psoriasis (PsO) or PsA (PsA+ vs. PsO-/PsA- cohorts) in the United States.
2. Estimate the burden of HZ in terms of healthcare resource utilization (HRU) and costs among adult PsA patients with vs. without HZ (PsA+/HZ+ vs. PsA+/HZ- cohorts).

Insurance claims (Oct 2015 – Feb 2020) were retrospectively analyzed. Generalized linear models were used to compare outcomes, adjusting for propensity scores and differences in relevant baseline characteristics.

Results

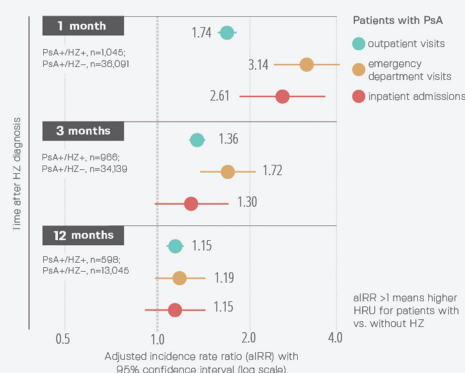
HZ incidence

Patients with **PsA (PsA+)** are **1.23 times (95% CI: 1.16–1.30)** more likely to develop HZ than patients without PsO or PsA (PsO-/PsA-) after adjustment for baseline characteristics.

PsA+, n=57,126;
PsO-/PsA-, n=23,837,237

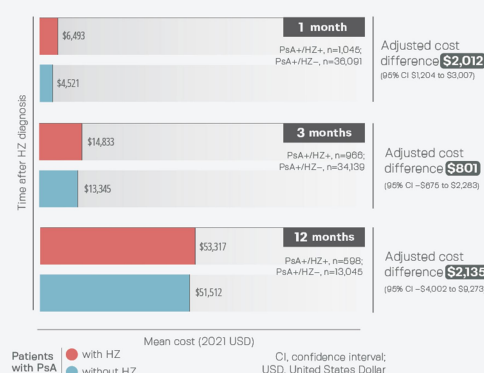
Healthcare resource utilization

HRU was significantly higher in patients with PsA and HZ (PsA+/HZ+) than in those with PsA without HZ (PsA+/HZ-) in the first month after HZ diagnosis.



Costs

All-cause costs were significantly higher in PsA+/HZ+ patients than in PsA+/HZ- patients in the first month after HZ diagnosis.



Conclusion

Patients with PsA had a higher incidence rate of HZ than those without PsO or PsA. All-cause HRU and costs among patients with PsA who developed HZ were substantial, highly variable, and mainly accumulated during the first month after HZ diagnosis.

Introduction

Psoriasis (PsO) is a chronic, inflammatory, immune-mediated disease that causes thick, red, scaly plaques on the skin¹ and affects around 3% of adults in the United States (US).² Approximately 20% of patients with PsO subsequently develop psoriatic arthritis (PsA),³ which causes inflammation of the joints, entheses, tendon sheaths, and axial skeleton.⁴ PsA can result in irreversible joint damage and impact physical function and quality of life.⁴ Risk factors for the development of PsA include more severe PsO, a family history of PsA/PsO, and musculoskeletal pain.⁴

Treatment options for patients with PsA include non-pharmacologic options (eg, weight loss, exercise), symptom control (eg, non-steroidal anti-inflammatory drugs, glucocorticoids), oral small molecules (eg, methotrexate and cyclosporine), biologics (eg, tumor necrosis factor [TNF] inhibitors and interleukin [IL] inhibitors), and Janus kinase (JAK) inhibitors.⁵ Patients with psoriatic disease are at increased risk of infection, not only due to their underlying disease but also because some of these treatments target the immune system.^{6–8}

Patients with psoriatic disease are also at increased risk of herpes zoster (HZ; shingles),⁸ which results from reactivation of the varicella zoster virus (VZV) that remains latent in the sensory ganglia after infection with varicella (chickenpox).⁹ When cellular immunity diminishes (due to advancing age or immunosuppression), latent VZV can reactivate, travel along the sensory nerves, and cause HZ.⁹ Patients with HZ typically have a painful blistering skin rash

and can go on to develop severe complications such as postherpetic neuralgia (PHN; long-standing pain at the rash site) or HZ ophthalmicus (which can cause keratitis, scarring, and even vision loss).^{9,10} HZ and its complications can result in impaired quality of life¹¹ and increased healthcare resource use (HRU) and costs.¹² The lifetime risk of HZ in the US population is approximately 33%,¹³ and risk increases considerably with age; the incidence rate doubles from around 5–6 cases per 1000 person-years (PY) for people in their 50s to 10–11 cases per 1000 PY for people in their 70s and 80s.¹⁴ Patients with PsA are at increased risk of HZ due to their underlying disease and the actions of some medications used to treat PsA, including systemic corticosteroids,^{15–19} JAK inhibitors,^{15,18,20,21} and TNF-alpha inhibitors.^{18,22}

In January 2018, the US Advisory Committee on Immunization Practices (ACIP) recommended recombinant zoster vaccine (RZV; *Shingrix*, GSK, Belgium) for immunocompetent adults aged ≥ 50 years.²³ In January 2022, an additional recommendation was published for RZV for immunodeficient or immunosuppressed adults aged ≥ 19 years.²⁴ Between these two ACIP recommendations, a 2019 publication from the Medical Board of the National Psoriasis Foundation recommended HZ vaccination for patients with PsA/PsO taking tofacitinib (a JAK inhibitor), systemic steroids, or combination systemic treatment due to their increased risk of HZ.¹⁵

To our knowledge, only two US studies have reported the incidence of HZ among patients with PsA, using data from 2007 to 2010⁸ and 2014 to 2018;¹⁶ and no studies have examined the HRU and costs associated with HZ among patients with PsA. The aims of the current study were, therefore, to (1) estimate and compare the incidence of HZ among adults with PsA vs without any psoriatic disease (PsA+ vs PsO–/PsA– cohorts) using recent, generalizable data and (2) estimate the burden of HZ in terms of all-cause HRU and costs among patients with PsA with vs without HZ (PsA+/HZ+ vs PsA+/HZ– cohorts). We also report HZ-related HRU and medical costs for patients in the PsA+/HZ+ cohort.

Materials and Methods

Data Source

We used data from October 1, 2015, through February 28, 2020, from Optum's de-identified Clinformatics Data Mart (CDM), which includes Commercial and Medicare Advantage with Part D health plan data from a geographically diverse population (all 50 states). It contains medical claims (including care in outpatient, emergency department [ED], and inpatient settings, etc.) and pharmacy claims. For further information, please see [Text S1](#).

Study Design

This retrospective, longitudinal, cohort study (GSK study identifier: VEO-000258) was conducted in two parts. The two parts of the study used separate cohorts based on separate inclusion and exclusion criteria to meet the study objectives. Part one estimated HZ incidence in PsA+ vs PsO–/PsA– cohorts. Part two estimated HRU and costs in PsA+/HZ+ and PsA+/HZ– cohorts. The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for HZ, PsA, and PsO are detailed in [Table S1](#).

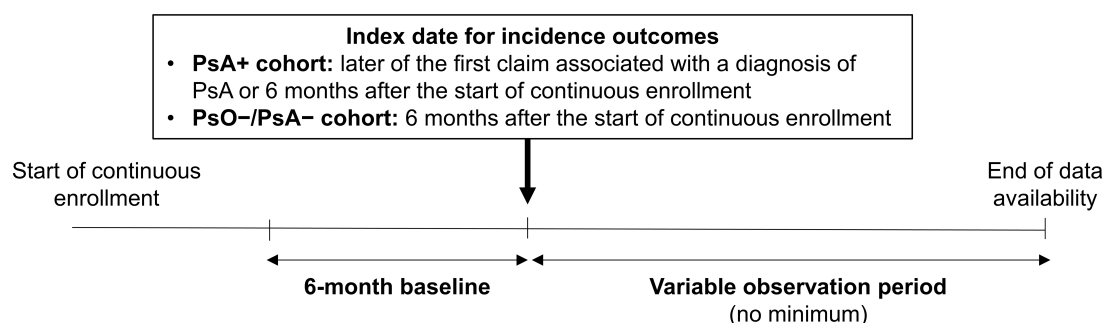
For the assessment of HZ incidence, the index date was defined as 6 months after the start of continuous enrollment (PsO–/PsA– cohort) or the later of the date of first PsA diagnosis or 6 months after the start of continuous enrollment (PsA+ cohort). Baseline was the 6 months before index, and there was no minimum follow-up time ([Figure 1A](#)). Patients were followed until the first of: incident HZ (event), HZ vaccination (censor), or end of data availability (censor).

For the assessment of HRU and costs, the index date was defined as the first HZ diagnosis during October 1, 2016, through January 28, 2020, for the PsA+/HZ+ cohort. The index date was randomly assigned based on the distribution of pre-index eligibility in the PsA+/HZ+ cohort for the PsA+/HZ– cohort. Baseline was the 12 months before index, and follow-up was the 1–12 months after index ([Figure 1B](#)).

Inclusion Criteria

Inclusion criteria for the PsA+ and PsO–/PsA– cohorts were (1) ≥ 6 months of continuous eligibility before the index date; (2) no claim for an HZ diagnosis (including HZ complications) before/on the index date; (3) no claim for an HZ vaccine before/on the index date; and (4) age ≥ 18 years on the index date. Patients in the PsA+ cohort had to have a confirmed diagnosis of PsA, defined as ≥ 1 medical claim with a diagnosis of PsA and another medical claim (≥ 30 days

A



B

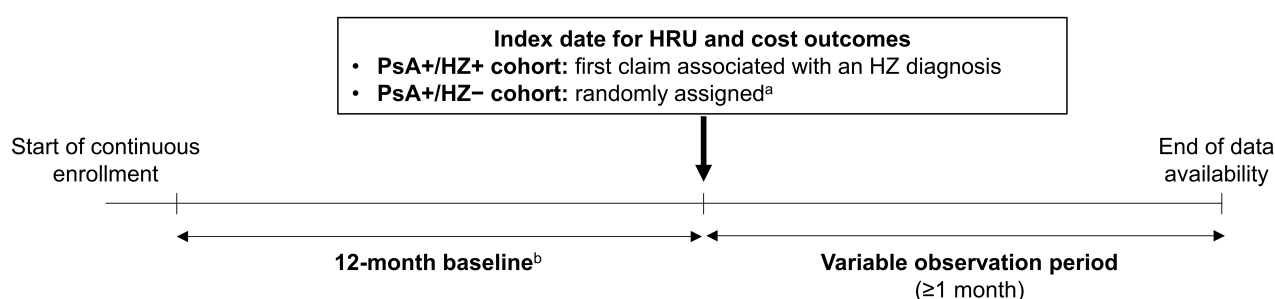


Figure 1 Study designs for the assessment of (A) HZ incidence (PsA+ and PsO-/PsA- cohorts) and (B) HRU and costs (PsA+/HZ+ and PsA+/HZ- cohorts).

Notes: ^aBased on the distribution of the pre-index eligibility (ie, time between beginning of continuous enrollment and index date) in the PsA+/HZ+ cohort. ^bPatients had to have ≥1 claim associated with a PsA diagnosis during 12-month baseline.

Abbreviations: HRU, healthcare resource use; HZ, herpes zoster; PsA, psoriatic arthritis; PsA+, patients with psoriatic arthritis; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; PsA+/HZ-, patients with psoriatic arthritis but without herpes zoster; PsO-/PsA-, patients with neither psoriatic arthritis nor psoriasis.

apart) associated with a diagnosis of PsA or PsO. Patients in the PsO-/PsA- cohort could not have any claims associated with diagnoses of PsA or PsO.

Inclusion criteria for the PsA+/HZ+ and PsA+/HZ- cohorts were (1) a confirmed diagnosis of PsA, defined as ≥1 medical claim associated with a diagnosis of PsA and another medical claim (≥30 days apart) associated with a diagnosis of PsA or PsO, including one during the 12-month baseline period; (2) continuous eligibility for ≥12 months before and ≥1 month after the index date; (3) no claim for an HZ vaccine before/on the index date; and (4) age ≥18 years on the index date. Patients in the PsA+/HZ+ cohort were required to have ≥1 claim associated with an HZ diagnosis (the first of which could not be for HZ with other nervous system involvement [ICD-10-CM: B02.2]) on a day not associated with HZ vaccination.

Study Variables

Baseline characteristics include demographic characteristics at index (age, sex, race/ethnicity, geographic region, insurance type) and clinical characteristics during 6- or 12-month baseline (Charlson comorbidity index [CCI],²⁵ rheumatoid arthritis, comorbidities potentially associated with HZ, additional immunosuppressive conditions, PsA/PsO-related treatments, and all-cause direct healthcare costs).

HZ incidence outcomes include unadjusted incidence rates of HZ and adjusted incidence rate ratios (aIRRs) for the overall population and stratified by age at index (18–49, 50–64, and ≥65 years) in the PsA+ vs PsO-/PsA- cohorts. HZ incidence rates and aIRRs for the PsA+ cohort vs the PsO-/PsA- cohort are also reported by PsA/PsO-related therapy in the PsA+ cohort (ie, phototherapy, systemic biologics [IL-17, -23, and -12/23 inhibitors, TNF-alpha inhibitors, and

T-cell inhibitor], systemic non-biologics, JAK inhibitors, and other [including topicals, systemic corticosteroids, no therapy]) used prior to the end of follow-up as defined by incident HZ, HZ vaccination, or end of data availability.

HRU outcomes include (1) all-cause HRU (outpatient visits, ED visits, and inpatient admissions) in the PsA+/HZ+ vs PsA+/HZ- cohorts; (2) all-cause costs, comprised of medical costs (outpatient, ED, inpatient, and other [eg, skilled nursing facilities, home care services, hospice, vision care, and durable medical equipment]) and pharmacy costs, in the PsA+/HZ+ vs PsA+/HZ- cohorts; and (3) HZ-related HRU and medical costs in the PsA+/HZ+ cohort (identified using an HZ diagnosis in any position on claims; diagnosis codes were only available for medical claims). These were measured during the first 1, 3, and 12 months after index among patients with ≥ 1 , ≥ 3 , and ≥ 12 months of follow-up, respectively. All-cause HRU and costs at 1 and 3 months are also reported among patients with ≥ 12 months of observation. All costs were adjusted to 2021 US dollars (USD) using the medical care component of the Consumer Price Index.²⁶

Statistical Analyses

All statistical analyses were conducted using the statistical software SAS Enterprise Guide 7.1 and SAS Studio (SAS Institute Inc., Cary, North Carolina, US).

Comparisons between the baseline characteristics of the PsA+ vs PsO-/PsA- and PsA+/HZ+ vs PsA+/HZ- cohorts were conducted using standardized differences, with thresholds of 20%, 50%, and 80% taken to represent small, medium, and large differences, respectively.^{27,28}

To account for potential differences between cohorts, multivariable comparative analyses were performed using doubly robust propensity score adjustment. Propensity scores were calculated using logistic regression with PsA or HZ status as the dependent variable for the incidence and HRU/costs analyses, respectively. Relevant baseline clinical and demographic characteristics were used as independent variables in the model. For further information, please see [Text S2](#).

Unadjusted HZ incidence rates were calculated by dividing the number of patients with HZ by the total person time observed from index to incident HZ, HZ vaccination, or end of data availability, and are reported per 1000 PY. aIRRs and their 95% confidence intervals (CIs) were calculated using generalized linear models (GLMs) assuming a Poisson distribution and log link, including propensity score of being diagnosed with PsA and relevant baseline characteristics as covariates, as detailed under each Figure that reports the related results. When over-dispersion was observed, negative binomial regression models were used instead of Poisson models. Significance was assumed for aIRRs when the 95% CIs did not include 1.

HRU outcomes are reported as the mean per-person number of each encounter type during the first 1, 3, and 12 months after index. These were compared using aIRRs, which were calculated as detailed above, but accounting for the propensity score of being in the PsA+/HZ+ cohort. Significance was assumed for aIRRs when the 95% CIs did not include 1.

Costs are reported as the mean \pm standard deviation (SD) total, mean medical (ie, outpatient visits, ED visits, inpatient admissions, and other visits), and mean pharmacy per-patient costs during the first 1, 3, and 12 months after index. Cost differences were estimated using a two-part modeling approach. Firstly, the probability of observing a positive cost was modeled using logistic regression. Secondly, a GLM with a gamma distribution and log link was used to predict costs among those with positive costs. Both models included the patients' propensity scores and relevant baseline characteristics, which are detailed under each Figure that reports the related results. The 95% CIs for the adjusted cost differences were estimated from nonparametric bootstrap procedures with 499 replications. Significance was assumed for adjusted cost differences when the 95% CIs did not include 0.

Results

HZ Incidence

From the 38,113,848 patients identified in CDM from October 1, 2015 to February 28, 2020, 57,126 were included in the PsA+ cohort and 23,837,237 in the PsO-/PsA- cohort ([Figure S1](#)). Patients in the PsA+ vs PsO-/PsA- cohort were older (mean age: 57.4 vs 49.7 years), had a higher comorbidity burden (mean CCI: 0.8 vs 0.4), more frequently had a diagnosis of

Table 1 Demographic Characteristics at Index

	Cohorts for HZ incidence			Cohorts for HRU and costs		
	PsA+ (n = 57,126)	PsO-/PsA- (n = 23,837,237)	Standardized difference ^a	PsA+/HZ+ (n = 1045)	PsA+/HZ- (n = 36,091)	Standardized difference ^a
Age, years, mean \pm SD	57.4 \pm 14.0	49.7 \pm 18.7	46.7%	63.5 \pm 13.1	59.0 \pm 14.3	33.2%
18–49, n (%)	16,847 (29.5)	12,229,065 (51.3)	44.5%	160 (15.3)	9629 (26.7)	27.9%
50–64, n (%)	20,691 (36.2)	5,255,582 (22.0)	31.2%	349 (33.4)	12,837 (35.6)	4.6%
≥ 65 , n (%)	19,588 (34.3)	6,352,590 (26.6)	16.6%	536 (51.3)	13,625 (37.8)	27.2%
Female, ^b n (%)	31,663 (55.4)	12,220,226 (51.3)	8.3%	662 (63.3)	19,676 (54.5)	18.0%
Race/ethnicity, n (%)						
White	42,973 (75.2)	14,970,006 (62.8)	26.9%	823 (78.8)	27,525 (76.3)	6.0%
Hispanic	5630 (9.9)	3,079,925 (12.9)	9.6%	109 (10.4)	3624 (10.0)	1.3%
Black	3445 (6.0)	2,471,734 (10.4)	15.8%	54 (5.2)	2222 (6.2)	4.3%
Asian	1565 (2.7)	1,210,204 (5.1)	12.1%	23 (2.2)	1017 (2.8)	3.9%
Unknown	3513 (6.1)	2,105,368 (8.8)	10.2%	36 (3.4)	1703 (4.7)	6.4%
Geographic region, n (%)						
South	27,119 (47.5)	10,406,629 (43.7)	7.7%	501 (47.9)	16,801 (46.6)	2.8%
Midwest	12,554 (22.0)	5,402,117 (22.7)	1.6%	210 (20.1)	8116 (22.5)	5.8%
West	10,411 (18.2)	5,013,736 (21.0)	7.1%	209 (20.0)	6670 (18.5)	3.9%
Northeast	7000 (12.3)	2,492,213 (10.5)	5.7%	125 (12.0)	4485 (12.4)	1.4%
Other/unknown	42 (0.1)	522,542 (2.2)	20.0%	0	19 (0.1)	3.2%
Insurance type, n (%)						
Medicare Advantage	23,773 (41.6)	6,707,606 (28.1)	28.3%	581 (55.6)	15,785 (43.7)	23.7%
Commercial	33,353 (58.4)	17,129,631 (71.9)	28.3%	464 (44.4)	20,306 (56.3)	23.7%

Notes: ^aStandardized differences of 20%, 50%, and 80% represent small, medium, and large differences, respectively.^{27,28} For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the two cohorts (PsA+ vs PsO-/PsA- or PsA+/HZ+ vs PsA+/HZ-) by the pooled SD of both groups. The pooled SD was the square root of the average of the squared SDs. For categorical variables with two levels, the standardized difference was calculated using the following equation, where P_1 and P_2 were the respective proportions of participants in the two cohorts: $(P_1 - P_2) / \sqrt{p(1-p)}$, where $p = (P_1 + P_2) / 2$. ^bIncluding some patients of unknown sex, who were inputted as female (PsA+ n = 4; PsO-/PsA- n = 2220; PsA+/HZ- n = 3).

Abbreviations: HRU, healthcare resource use; HZ, herpes zoster; PsA+, patients with psoriatic arthritis; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; PsA+/HZ-, patients with psoriatic arthritis but without herpes zoster; PsO-/PsA-, patients with neither psoriatic arthritis nor psoriasis; SD, standard deviation.

rheumatoid arthritis (RA) (15.2% vs 0.9%), more often used systemic PsA/PsO-related treatments or phototherapy (64.6% vs 11.5%), and had higher mean all-cause healthcare costs during baseline (\$20,711 vs \$6102) (Tables 1 and 2). The mean \pm standard deviation lengths of the observation periods in the PsA+ and PsO-/PsA- cohorts were 21.3 ± 14.8 and 21.7 ± 16.0 months, respectively.

There were 1427 HZ events during 96,117 PY of follow-up in the PsA+ cohort and 318,864 HZ events during 41,557,883 PY in the PsO-/PsA- cohort. Overall, the incidence of HZ was higher in the PsA+ vs PsO-/PsA- cohort (14.85 vs 7.67 per 1000 PY; aIRR: 1.23; 95% CI: 1.16–1.30) (Figure 2). The incidence rate of HZ increased with age, from 9.88 to 18.81 per 1000 PY for those aged 18–49 to ≥ 65 years, respectively, in the PsA+ cohort and from 3.92 to 11.91 per 1000 PY, respectively, in the PsO-/PsA- cohort. When stratified by age groups, HZ incidence was significantly higher in the PsA+ vs PsO-/PsA- cohorts after adjustment in the youngest and oldest age groups.

Table 2 Baseline Clinical Characteristics

	Cohorts for HZ incidence			Cohorts for HRU and costs		
	PsA+ (n = 57,126)	PsO-/PsA- (n = 23,837,237)	Standardized difference ^a	PsA+/HZ+ (n = 1045)	PsA+/HZ- (n = 36,091)	Standardized difference ^a
Clinical characteristics during 6-month (incidence cohorts) or 12-month (HRU/costs cohorts) baseline						
CCI, ^b mean ± SD	0.8 ± 1.3	0.4 ± 1.0	37.2%	1.5 ± 1.9	1.2 ± 1.7	18.9%
Rheumatoid arthritis n (%)	8687 (15.2)	221,333 (0.9)	52.4%	252 (24.1)	6772 (18.8)	13.0%
Comorbidities potentially associated with HZ, ^c n (%)	6998 (12.3)	1,102,816 (4.6)	27.4%	221 (21.1)	6186 (17.1)	10.2%
Additional immunosuppressive conditions, ^d n (%)	4453 (7.8)	490,870 (2.1)	26.5%	123 (11.8)	3108 (8.6)	10.4%
PsA/PsO-related treatments during 6-month (incidence cohorts) or 12-month (HRU/cost cohorts) baseline, n (%)						
Systemic non-biologics	26,843 (47.0)	2,709,257 (11.4)	78.4%	627 (60.0)	20,205 (56.0)	8.1%
Systemic corticosteroids	18,692 (32.7)	2,659,778 (11.2)	52.1%	561 (53.7)	16,244 (45.0)	17.4%
Systemic biologics	18,150 (31.8)	58,875 (0.2)	86.0%	402 (38.5)	14,530 (40.3)	3.7%
Topical steroids	15,478 (27.1)	774,110 (3.2)	66.5%	391 (37.4)	13,673 (37.9)	1.0%
Non-steroidal topicals	1631 (2.9)	12,911 (0.1)	23.4%	43 (4.1)	1502 (4.2)	0.2%
Phototherapy	593 (1.0)	3426 (0.0)	14.1%	19 (1.8)	578 (1.6)	1.7%
Systemic JAK inhibitors	185 (0.3)	3295 (0.0)	7.6%	19 (1.8)	308 (0.9)	8.4%
PsA/PsO-related treatments at index, ^e n (%)						
Systemic non-biologics	19,600 (34.3)	1,227,462 (5.1)	73.3%	380 (36.4)	12,215 (33.8)	5.3%
Systemic corticosteroids	7719 (13.5)	791,412 (3.3)	36.7%	185 (17.7)	4394 (12.2)	15.5%
Systemic biologics	17,761 (31.1)	57,554 (0.2)	84.9%	360 (34.4)	13,149 (36.4)	4.1%
Topical steroids	6820 (11.9)	264,984 (1.1)	43.8%	112 (10.7)	4094 (11.3)	2.0%
Non-steroidal topicals	711 (1.2)	5250 (0.0)	15.4%	13 (1.2)	440 (1.2)	0.2%
Phototherapy	324 (0.6)	1753 (0.0)	10.5%	10 (1.0)	195 (0.5)	4.8%

(Continued)

Table 2 (Continued).

	Cohorts for HZ incidence			Cohorts for HRU and costs		
	PsA+ (n = 57,126)	PsO-/PsA- (n = 23,837,237)	Standardized difference ^a	PsA+/HZ+ (n = 1045)	PsA+/HZ- (n = 36,091)	Standardized difference ^a
Systemic JAK inhibitors	178 (0.3)	3154 (0.0)	7.4%	19 (1.8)	239 (0.7)	10.4%
All-cause direct healthcare costs during 6-month (incidence cohorts) or 12-month (HRU/cost cohorts) baseline, 2021 USD, mean ± SD	20,711 ± 39,041	6102 ± 28,538	42.7%	57,141 ± 92,537	48,510 ± 72,473	10.4%

Notes: ^aSee Table 1 footnote. ^bCCI was computed according to the methods outlined in Quan et al.²⁵ ^cAsthma, Crohn's disease, idiopathic pulmonary fibrosis or interstitial lung disease, ulcerative colitis, multiple sclerosis, other giant cell arteritis, Sicca syndrome, ankylosing spondylitis, sarcoidosis, Wegener's granulomatosis, and scleroderma. ^dMainly use of chemotherapy for solid and hematological malignancies in prior 6 months. ^eWithin the 3 months before index or initiated before and ended after index (for biologics and JAK inhibitors) or within 6 months before and covering index (other treatments). A 30-day extension following the date of discontinuation was applied to the observation window for all medication groups.

Abbreviations: CCI, Charlson-Quan Comorbidity Index; HRU, healthcare resource use; HZ, herpes zoster; JAK, Janus kinase; PsA, psoriatic arthritis; PsA+, patients with psoriatic arthritis; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; PsA+/HZ-, patients with psoriatic arthritis but without herpes zoster; PsO-/PsA-, patients with neither psoriatic arthritis nor psoriasis; PsO, psoriasis; SD, standard deviation; USD, United States dollars.

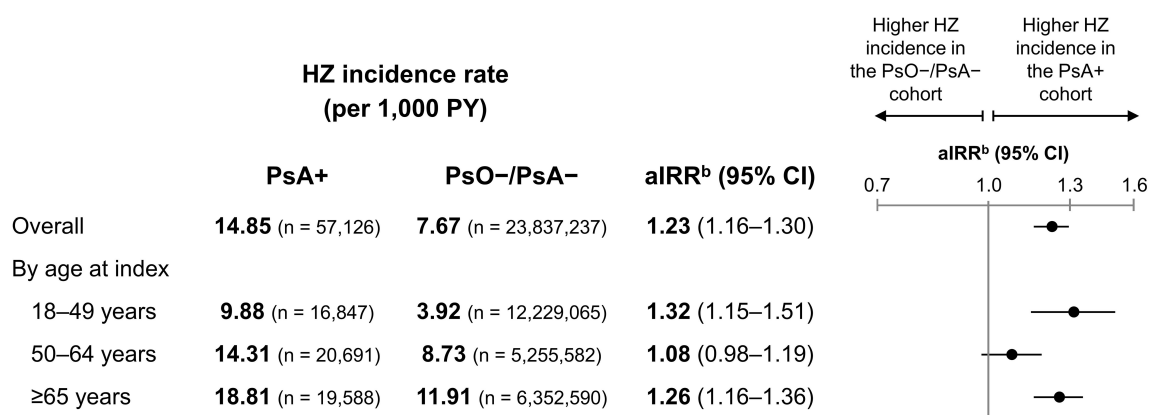


Figure 2 Unadjusted incidence rates and aIRRs of HZ in the PsA+ vs PsO-/PsA- cohorts. ^aOverall and by age at index.

Notes: ^aThe mean \pm SD observation period in the PsA+ cohort was 20.2 \pm 14.4 months (18.4 \pm 14.0, 19.4 \pm 14.3, 22.6 \pm 14.7 months across age groups); in the PsO-/PsA- cohort 20.9 \pm 15.7 months (18.2 \pm 14.8, 20.2 \pm 15.4, 26.8 \pm 16.0 months across age groups). ^baIRRs were calculated using the PROC GENMOD procedure for GLMs assuming a Poisson distribution and log link, accounting for the propensity score of being diagnosed with PsA and relevant baseline characteristics. The GLM for the overall cohort adjusted for propensity score based on the following baseline characteristics: index year, age at index, sex, race, region, insurance type, CCI, any comorbidity associated with HZ, additional immunosuppressive conditions, use of specific PsO/PsA treatment type, inpatient costs, outpatient costs, ED costs, other medical costs, and pharmacy costs, as well as the same characteristics excluding sex (doubly robust adjustment). For the age stratifications, age at index was excluded from the propensity score and doubly robust adjustment by design.

Abbreviations: aIRR, adjusted incidence rate ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; ED, emergency department; GLM, generalized linear model; HZ, herpes zoster; PsA, psoriatic arthritis; PsA+, patients with psoriatic arthritis; PsO, psoriasis; PsO-/PsA-, patients with neither psoriatic arthritis nor psoriasis; PY, person-years; SD, standard deviation.

The incidence rate of HZ varied widely by PsA/PsO-related therapy (from 3.18 to 28.75 per 1000 PY) as shown in [Figure S2](#), although the low numbers of events and patients in some groups should be noted.

HRU and Costs

Overall, 1045 and 36,091 patients were included in the PsA+/HZ+ and PsA+/HZ- cohorts, respectively ([Figure S3](#)). Patients in the PsA+/HZ+ vs PsA+/HZ- cohort were older (mean age: 63.5 vs 59.0 years) and were more often on Medicare Advantage plans (55.6% vs 43.7%) ([Tables 1](#) and [2](#)). Follow-up was available for ≥ 3 months for 966 patients (92.4%) in the PsA+/HZ+ cohort and 34,139 patients (94.6%) in the PsA+/HZ- cohort, and for ≥ 12 months for 598 patients (57.2%) and 13,045 patients (36.1%), respectively.

The per-person numbers of outpatient visits, ED visits, and inpatient admissions were all significantly higher in the PsA+/HZ+ vs PsA+/HZ- cohorts during the first month after index (eg, outpatient: 3.04 vs 1.61 visits; aIRR: 1.74; 95% CI: 1.63–1.86; [Figure 3](#)). During the first 3 months after index, outpatient visits and ED visits were significantly higher in the PsA+/HZ+ cohort; during the first 12 months, only outpatient visits were significantly higher. When the analysis was restricted to patients with ≥ 12 months of follow-up, all three HRU outcomes were significantly higher in the PsA+/HZ+ vs PsA+/HZ- cohorts during the first 1 and 3 months ([Figure S4](#)).

Mean all-cause per-patient costs during the first month after index were significantly higher in the PsA+/HZ+ vs PsA+/HZ- cohorts (\$6493 vs \$4521; adjusted cost difference: \$2012; 95% CI: \$1204–\$3007; [Figure 4A](#)). This was driven by a significant difference in inpatient costs (adjusted cost difference: \$1074; 95% CI: \$584–\$1761), but the adjusted cost differences in outpatient and ED costs were also significant (outpatient: \$288; 95% CI: \$57–\$541; ED: \$233; 95% CI: \$165–\$344). During the 3 months after index, overall costs were numerically higher in the PsA+/HZ+ vs PsA+/HZ- cohort (\$14,833 vs \$13,345; adjusted cost difference: \$801; 95% CI: –\$675 to \$2283; [Figure 4B](#)). However, the adjusted cost differences in outpatient and ED costs were significant (outpatient: \$649; 95% CI: \$105–\$1246; ED: \$260; 95% CI: \$117–\$441). By 12 months after index, the adjusted total cost difference was \$2135, but the 95% CI was very wide, at –\$4002 to \$9273 ([Figure 4C](#)).

When the analysis was restricted to patients with ≥ 12 months of follow-up, the adjusted cost differences between the PsA+/HZ+ vs PsA+/HZ- cohorts were statistically significant during the first 1 and 3 months (1 month: \$2993; 95% CI

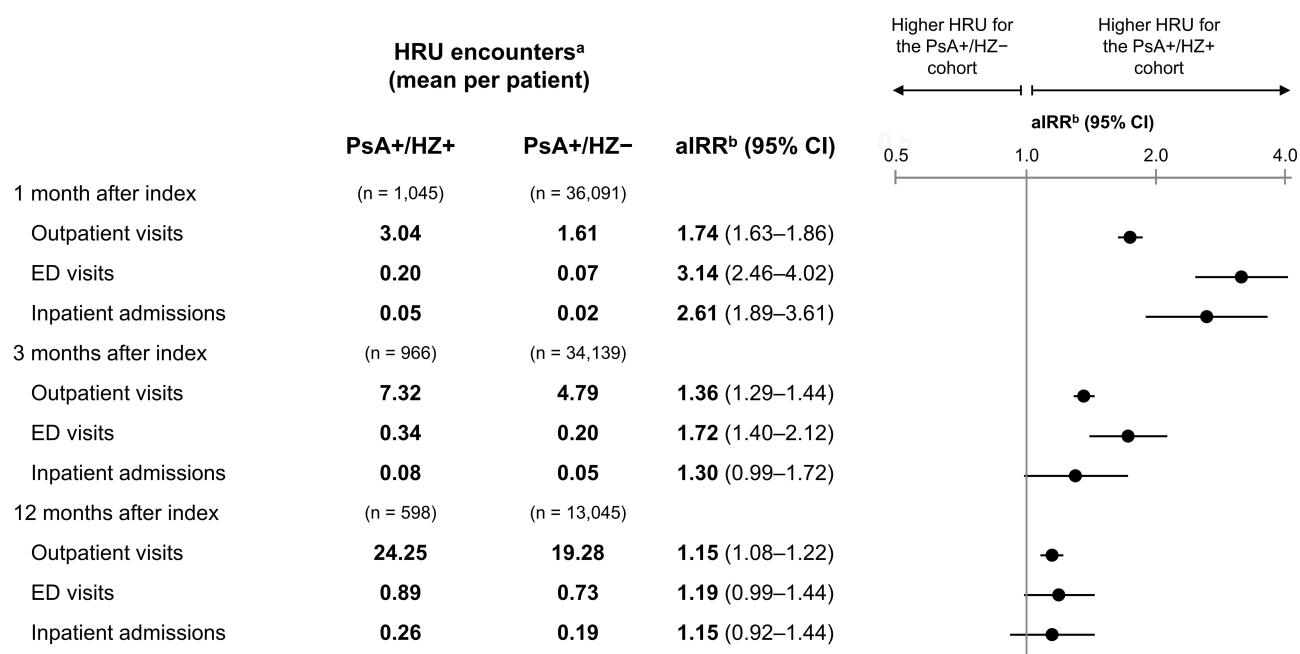


Figure 3 HRU in the PsA+/HZ+ vs PsA+/HZ- cohorts during the first 1, 3, and 12 months after index.

Notes: ^aHRU encounters were calculated as the average number of HRU events per patient during the period of interest. ^baIRRs were calculated using the PROC GENMOD procedure for GLMs assuming a negative binomial distribution and log link, accounting for the propensity score of being in the PsA+/HZ+ cohort (for the PsA+/HZ- cohort) and relevant baseline characteristics. The GLM adjusted for a propensity score based on the following baseline characteristics: index year, age at index, sex, race, region, insurance type, having only one PsO or PsA diagnosis prior to index, CCI, any comorbidity associated with HZ, additional immunosuppressive conditions, use of specific PsO/PsA treatment type, inpatient costs, outpatient costs, ED costs, other medical costs, and pharmacy costs, as well as the following characteristics (doubly robust adjustment): age at index, inpatient costs, outpatient costs, ED costs, other medical costs, and pharmacy costs.

Abbreviations: aIRR, adjusted incidence rate ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; ED, emergency department; GLM, generalized linear model; HRU, healthcare resource use; HZ, herpes zoster; PsA, psoriatic arthritis; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; PsA+/HZ-, patients with psoriatic arthritis but without herpes zoster; PsO, psoriasis.

\$1688–\$4608; 3 months: \$2862; 95% CI \$693–\$5169), but not during the first 12 months (\$2135; 95% CI: –\$4002 to \$9273) (Figure S5).

In the PsA+/HZ+ cohort, mean HZ-related medical costs were \$1600, \$1660, and \$1798 during the first 1, 3, and 12 months after index, respectively (Figure 5). Costs were driven by inpatient costs, but most HZ-related HRU were outpatient visits (1.42–2.07 per patient across the three time periods; compared to 0.12–0.14 ED visits; and 0.03–0.04 inpatient admissions; data not shown).

Discussion

This retrospective claims-based study estimated that the incidence of HZ was significantly higher in patients with PsA vs those without psoriatic disease (14.85 vs 7.67 per 1000 PY; aIRR: 1.23; 95% CI: 1.16–1.30). Also, it was found that among patients with PsA, HRU and costs were significantly higher among those with HZ as compared to those without HZ during the first month after index (adjusted cost difference: \$2012; 95% CI: \$1204–\$3007).

HZ Incidence

Our finding that patients with PsA had a higher crude incidence of HZ than those without psoriatic disease (14.85 vs 7.67 per 1000 PY) is in line with an earlier claims database study from the US, which reported age/sex-standardized incidence rates of approximately 10.3 vs 5.3 cases per 1000 PY among patients with PsA vs healthy individuals during 2007–2010.⁸ The HZ incidence in our PsA+ cohort is likely higher than in the PsA cohort in the previous study⁸ as our PsA+ cohort was older than the US census population that the previous study was standardized to. In the previous study,⁸ the HZ incidence among patients with PsA aged 51–60 years was 13.2 per 1000 PY, which is similar to the incidence in the current population of patients with PsA, who had a mean age of 57.4 years. The HZ incidence in our PsO–/PsA–

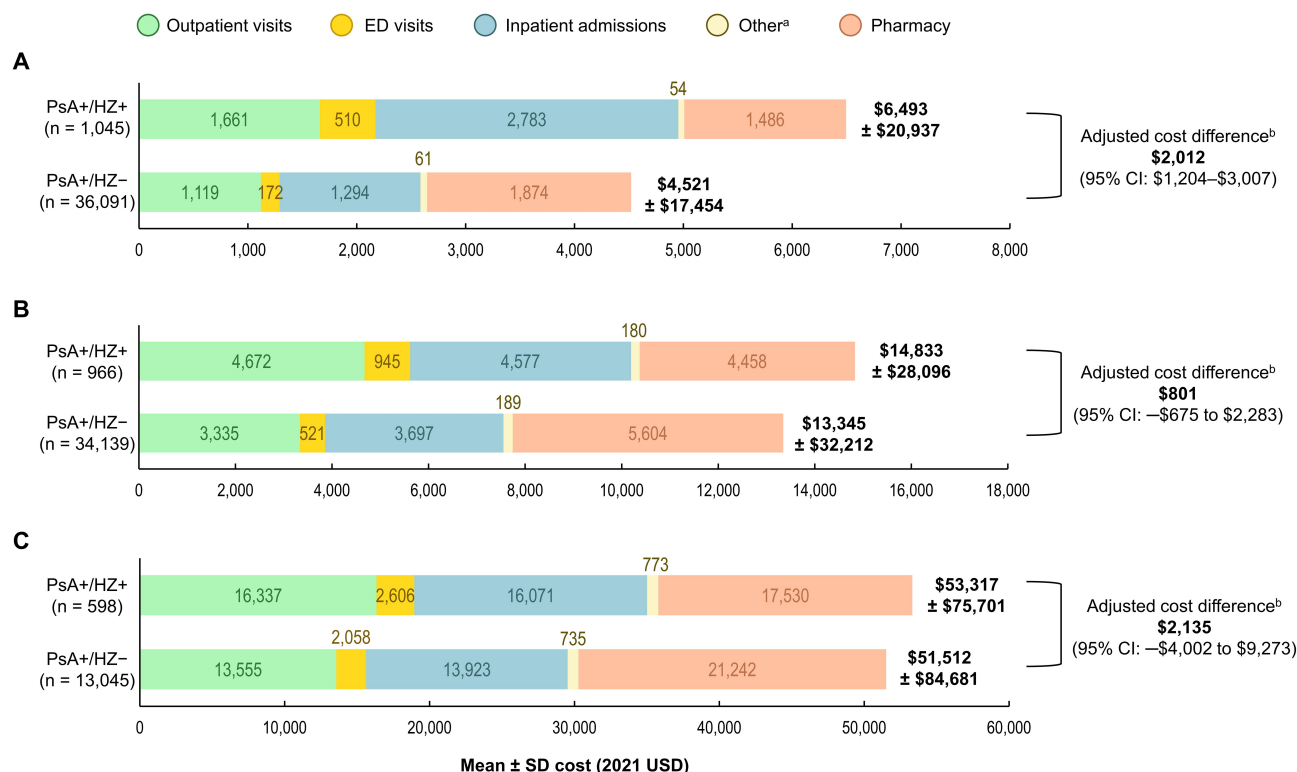


Figure 4 All-cause mean per-patient costs in the PsA+/HZ+ vs PsA+/HZ- cohorts during the first (A) 1 month, (B) 3 months, and (C) 12 months after index.

Notes: ^aIncluding skilled nursing facilities, home care services, hospice, vision care, and durable medical equipment. ^bAdjusted cost differences were estimated using the two-part modeling approach: (1) the probability of observing a positive cost was modeled using logistic regression; (2) a GLM with a gamma distribution and log link was used to predict costs among patients with positive costs. Both models included the patients' propensity scores and relevant baseline characteristics. The 95% CIs were estimated from nonparametric bootstrap procedures with 499 replications. The GLM adjusted for a propensity score based on the following baseline characteristics: index year, age at index, sex, race, region, insurance type, having only one PsO or PsA diagnosis prior to index, CCI, any comorbidity associated with HZ, additional immunosuppressive conditions, use of specific PsO/PsA treatment type, inpatient costs, outpatient costs, ED costs, other medical costs, and pharmacy costs, as well as the following characteristics (doubly robust adjustment): age at index, insurance type, inpatient costs, outpatient costs, ED costs, other medical costs, and pharmacy costs.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; ED, emergency department; GLM, generalized linear model; HZ, herpes zoster; PsA, psoriatic arthritis; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; PsA+/HZ-, patients with psoriatic arthritis but without herpes zoster; PsO, psoriasis; SD, standard deviation; USD, United States Dollars.

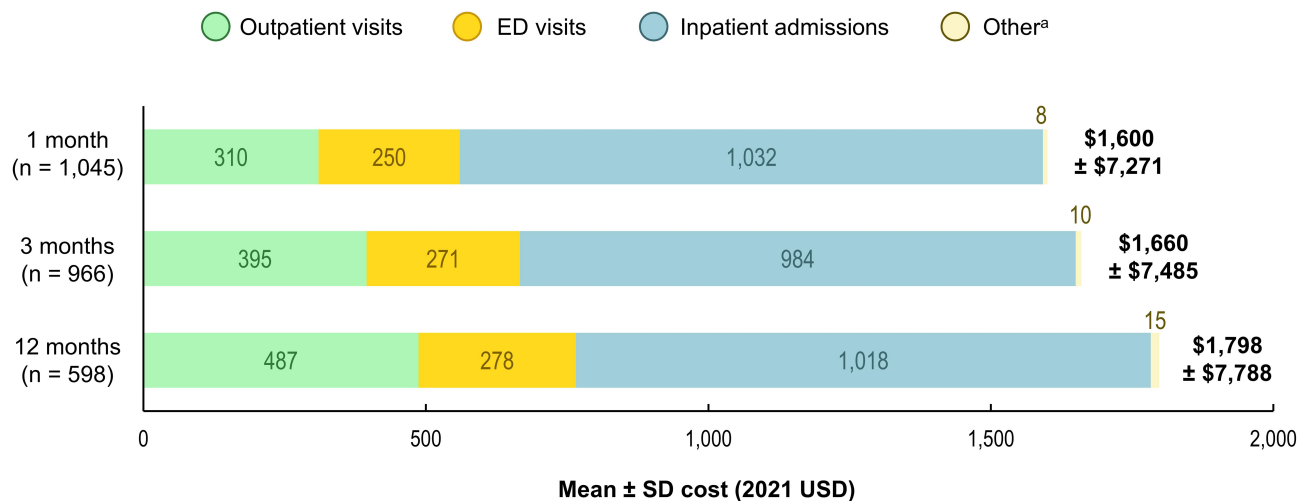


Figure 5 HZ-related mean per-patient medical costs in the PsA+/HZ+ cohort during the first 1, 3, and 12 months after index.

Notes: ^aIncluding skilled nursing facilities, home care services, hospice, vision care, and durable medical equipment.

Abbreviations: ED, emergency department; HZ, herpes zoster; PsA+/HZ+, patients with psoriatic arthritis and herpes zoster; SD, standard deviation; USD, United States Dollars.

cohort is probably higher than in the healthy cohort in the previous study⁸ as some patients in our PsO-/PsA- cohort had comorbidities that were excluded from the healthy cohort in the previous study (eg, diabetes, RA). Various studies have also reported an increased risk of HZ among patients with vs without PsO.^{29–32}

In the above-mentioned US study, patients with PsA had a slightly higher age/sex-standardized incidence of HZ than patients with PsO (approximately 10.3 vs 9.2 per 1000 PY).⁸ We also found a numerically higher incidence of HZ among the current PsA+ population vs a PsO+ population in our previous study that used similar methodology (14.85 vs 11.35 per 1000 PY).³³ Another US claims database study has also reported a slightly higher HZ incidence among patients with PsA vs PsO (9.6 vs 8.2 per 1000 PY) among patients who were receiving various systemic treatments.¹⁶

The incidence rates of HZ increased with age in both the PsA+ and PsO-/PsA- cohorts, which is in line with other studies of patients with PsA,⁸ PsO,^{8,29,31,32} and the general population.¹⁴ For example, a database study from the US (2005–2009) reported that the incidence of HZ increased from 5.3 to 15.4 per 1000 PY among patients with PsO aged 18–49 to ≥65 years.²⁹ Similarly, a worldwide meta-regression has reported that the HZ incidence increases from 5.2 cases per 1000 PY for the general population aged 50–54 years to 11.3 cases per 1000 PY for those aged ≥85 years.¹⁴ These results indicate that older patients – including those with psoriatic disease – have a greater HZ disease burden.

In the PsA+ cohort, HZ incidence varied widely by PsA/PsO-related therapy ([Figure S2](#)), although these data should be interpreted with caution due to confounding factors (eg, the correlation between disease severity and prescribed therapies), small event and patient numbers in some groups, and because groupings were only based on the medications used at the end of the observation period. We found that PsA+ patients on IL-23, IL-17, or T-cell inhibitors had lower or similar HZ incidences to the PsO-/PsA- cohort, while those on any other therapy had higher HZ incidences vs the PsO-/PsA- cohort. Other studies have reported that HZ risk is increased in patients with psoriatic disease taking systemic corticosteroids,^{15–19} JAK inhibitors,^{15,18,20,21} TNF-alpha inhibitors,^{18,22} and various combination treatments,^{15,16,18,19} but not medications targeting interleukins.^{15,16,18,34}

HRU and Costs

Patients in the PsA+/HZ+ cohort had significantly more outpatient visits, ED visits, and inpatient admissions during the first month after index than those in the PsA+/HZ- cohort, which resulted in a significant adjusted total cost difference (\$2012; 95% CI: \$1204–\$3007). During the first 3 and 12 months after index, the adjusted cost differences were \$801 and \$2135, respectively, but the 95% CIs were wide (–\$675 to \$2283 and –\$4002 to \$9273, respectively). This is likely due to high variability in costs. Most of the HZ-related cost was accrued during the first month after index (mean cost \$1600). Among patients with longer follow-up, mean HZ-related costs during the first 3 and 12 months were not considerably higher. This is not surprising as HZ is generally an acute disease; however, patients who went on to develop complications such as PHN or HZ ophthalmicus may have required longer-term medical care and incurred additional longer-term costs. It is worth noting that patients in the PsA+/HZ+ cohort had higher mean baseline medical costs than those in the PsA+/HZ- cohort (\$57,141 vs \$48,510), which likely reflects a greater morbidity but may also include some HRU for HZ before this had been diagnosed, although these were adjusted for in the analyses presented.

It is our belief that ours is the first study to report on the HRU and costs of HZ among patients with PsA. However, two studies from the US have reported annual mean all-cause healthcare costs of \$23,427 (2014 USD)³⁵ and \$29,742 (2019 USD)³⁶ per patient with PsA. The mean annual costs in our PsA+/HZ- cohort of \$48,510 during baseline (n = 36,091) and \$51,512 during follow-up (n = 13,045) (2021 USD) were considerably higher than these estimates. Even accounting for inflation, costs in the current study were higher than those in the earlier studies, potentially due to the higher mean age (59 vs 47 or 48 years) and because we included patients with prevalent PsA, while the earlier studies aimed to identify patients with incident PsO/PsA.^{35,36}

Various studies from the US with similar designs to the current study have reported on the HRU and costs of HZ among adults with other inflammatory and autoimmune diseases, comparing these outcomes in adults with vs without HZ. Specific populations have included PsO,³³ RA,³⁷ Crohn's disease (CD),³⁸ and ulcerative colitis.³⁸ aIRRs for outpatient visits, ED visits, and inpatient admissions in the first month after HZ in the current study were in line with those from the other four populations (outpatient: 1.74 vs 1.64–1.96; ED: 3.14 vs 2.66–3.66; inpatient: 2.61 vs 2.19–3.43).^{33,37,38} Adjusted all-cause healthcare cost differences in the first month after HZ ranged from \$1390 (PsO+/HZ+ vs

PsO+/HZ– [2021 USD]) to \$3774 (CD+/HZ+ vs CD+/HZ– [2020 USD]),^{33,37,38} highlighting the high costs associated with HZ among patients with various inflammatory and autoimmune diseases.

Strengths and Limitations

Strengths of this study include the novelty of the HRU and cost findings, the recency of the data, and the breadth of the sample. Also, the robust analytical approach used for the comparative analyses allowed us to maximize the sample size, rather than using propensity score matched populations, which would have reduced the sample size and potentially the generalizability. Although multivariable models and doubly robust propensity score adjustment may arrive at similar conclusions, the latter is more robust to model misspecification.³⁹

Data were derived from CDM, which includes members with commercial and Medicare Advantage with Part D plans. The results may, therefore, not be generalizable to patients with other insurance programs, such as Medicaid, or to those without insurance. Administrative claims databases do not include detailed clinical measures (eg, disease severity, physician notes, patient-reported outcomes, or quality of life measures). The resulting lack of this information may have resulted in residual confounding and misclassification in the study. For example, patients in the PsA+ cohort were more likely to have a diagnosis of RA than those in the PsO–/PsA– cohort, but this may have been due to misdiagnoses of PsA or RA. The estimation of HRU and costs may also have been subject to coding errors, omissions, duplications, or missing data.

Patients with HZ may have a prodromal phase of disease before the typical rash appears, hence any HRU during the prodromal period (ie, before an HZ diagnosis) may not be associated with an HZ diagnosis.^{40,41} We only included HRU after an HZ diagnosis, which could have resulted in underestimation of HRU and costs in the PsA+/HZ+ cohort during the follow-up period. Some of these costs may have been included in the baseline all-cause cost, as this was higher in the PsA+/HZ+ vs PsA+/HZ– cohorts.

Lastly, although ICD-10-CM codes for acute HZ have high positive predictive values,⁴² it is possible that using a single claim associated with an HZ diagnosis may have resulted in a slight overestimation of HZ incidence.

Conclusions

Patients with PsA had a significantly higher incidence of HZ than those without psoriatic disease. Further, among patients with PsA, those who also had HZ had higher HRU and costs during the first month after an HZ diagnosis than those without HZ. Results from this study help to fill a gap in the literature; considering the burden of HZ among patients with PsA, the findings are important to understand the impact of HZ in this population and could be used to inform clinical decision-making regarding HZ prevention.

Abbreviations

ACIP, Advisory Committee on Immunization Practices; aIRR, adjusted incidence rate ratio; CCI, Charlson comorbidity index; CI, confidence interval; ED, emergency department; GLM, generalized linear model; HRU, healthcare resource use; HZ, herpes zoster; ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; IL, interleukin; JAK, Janus kinase; CDM, Clinformatics Data Mart; PHN, postherpetic neuralgia; PsA, psoriatic arthritis; PsO, psoriasis; PY, person-years; RZV, recombinant zoster vaccine; SD, standard deviation; TNF, tumor necrosis factor; US, United States; USD, United States dollar.

Trademark

Shingrix is a trademark owned by or licensed to GSK.

Data Sharing Statement

The data that support the findings of this study are available from Optum, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available.

Ethics Approval

This study complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred. Study results are aggregate analyses that omit subject identification; hence, informed consent, ethics committee, and institutional review board approval were not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors had full access to the data. The work described was carried out in accordance with the recommendations of the International Committee of Medical Journal Editors for conduct, reporting, editing, and publication of scholarly work in medical journals.

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Disclosure

David Singer, Nikita Stempniewicz, and Sara Poston are employees of, and hold financial equities in, GSK. Philippe Thompson-Leduc, Deepshikhar Gupta, Wendy Y. Cheng, Selvam R. Sendhil, Manasvi Sundar, Ella Hagopian, and Mei Sheng Duh are employees of Analysis Group, Inc., a consulting firm that has received funding from GSK for the conduct of this study. Siyu Ma declares to have received postdoctoral fellowship grant from GSK during the conduct of the study. The authors declare no other financial and non-financial relationships and activities for this work.

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