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ORIGINAL RESEARCH

Clinical and Economic Burden of Herpes Zoster in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study Using Administrative Claims

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ABSTRACT

Objective: To estimate the incremental healthcare resource utilization (HRU) and cost burden posed by herpes zoster (HZ) in adult patients with rheumatoid arthritis (RA) in the United States.

Methods: A retrospective cohort study was conducted using an administrative claims database containing commercial and Medicare Advantage with Part D data, between October 2015 and February 2020. Patients with RA and HZ (RA+/HZ+) or RA without HZ (RA+/HZ−) were identified based on diagnosis codes and relevant medications. Outcomes measured included HRU and medical, pharmacy, and total costs at month 1, quarter 1, and year 1 after the index date (HZ diagnosis for RA+/HZ+ cohort, randomly assigned for RA+/HZ− cohort). Generalized linear models incorporating propensity scores and other covariates were used to estimate differences in outcomes between cohorts.

Results: A total of 1866 patients from the RA+/HZ+ cohort and 38,846 patients from the RA+/HZ− cohort were included. Hospitalizations and emergency department visits occurred more frequently in the RA+/HZ+ than the RA+/HZ− cohort, especially in the month after HZ diagnosis (adjusted incidence rate ratio [95% confidence interval (CI)] for hospitalizations: 3.4 [2.8; 4.2]; emergency department visits: 3.7 [3.0; 4.4]). Total costs were also higher in the month after HZ diagnosis (mean adjusted cost difference [95% CI]: $3404 [$2089; $4779]), with cost differences driven by increased medical costs ($2677 [$1692; $3670]).

Conclusions: These findings highlight the high economic burden of HZ among individuals with RA in the United States. Strategies to reduce the risk of HZ in patients with RA (such as vaccination) may serve to reduce this burden.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-023-00549-x.

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Key Summary Points

Why carry out this study?

Patients with rheumatoid arthritis (RA) have a greater risk of herpes zoster (HZ) infection compared with the general adult population in the United States (US).

Despite evidence of this increased risk, there is a lack of data on the incremental economic burden of HZ among RA patients.

The study therefore aimed to estimate the incremental healthcare resource utilization (HRU) and cost burden posed by HZ in patients with RA in the US.

What was learned from the study?

Greater all-cause HRU and medical costs were observed in RA patients with HZ compared to RA patients without HZ following HZ diagnosis.

Economic burden was driven by increased medical costs, which were particularly associated with hospitalization and emergency department visits.

These results reflect a high healthcare need after HZ diagnosis among patients with RA and highlight the potential benefit of preventive interventions, including vaccination.

DIGITAL FEATURES

This article is published with digital features, including video abstract to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.22568200.

INTRODUCTION

Herpes zoster (HZ) is a painful viral infection caused by the reactivation of the varicella-zoster virus [1]. It is estimated that one out of every three individuals in the United States (US) will develop HZ during their lifetime, resulting in approximately 1 million cases each year [1]. HZ is associated with complications such as postherpetic neuralgia (PHN), which has been found to occur in up to a third of HZ patients, and HZ ophthalmicus (HZO), which occurs more rarely but can be severe [2, 3]. In some cases, these complications can result in additional sequelae and can have a further negative impact on patients' quality of life [1, 3, 4]. HZ has also been associated with high direct medical costs, and studies have estimated that the costs of treating HZ within the US may exceed $1 billion annually [5, 6].

Immunosenescence, or the natural decline in immune function with age that occurs among older adults, as well as immunosuppression due to disease or therapy, are both associated with an increased risk of HZ [1, 7–10]. As a result, patients with immunocompromising conditions (e.g., malignancy, solid organ transplant [SOT], or bone marrow or stem cell transplant [BMSCT]) have been reported to have higher relative risks of HZ compared with their immunocompetent counterparts [9, 10]. Moreover, the additional medical cost burden on individuals with immunocompromising conditions is further compounded by costs associated with HZ among this patient population. One study in the US reported that immunocompromised patients with HZ (including patients with malignancy, human immunodeficiency virus [HIV] infection, or transplantation) incurred higher medical costs and had greater use of pain medication, and inpatient, emergency department, and outpatient services, compared with immunocompromised patients without HZ [5, 11].

Rheumatoid arthritis (RA) is an example of an autoimmune disease that has been associated with a greater risk of HZ [12–14]; studies have previously reported the incidence of HZ in patients with RA to be 1.5–2.4 times greater

than the general adult population in the US [13, 14]. RA is also commonly treated with immunosuppressants such as Janus kinase inhibitors and glucocorticoids [15], which suppress the immune system and may consequently increase susceptibility of RA patients to developing HZ [12–14, 16, 17].

However, despite evidence that RA patients are at an increased risk of HZ and research demonstrating the higher incremental cost of HZ among immunocompromised populations, there are no estimates of the incremental healthcare resource utilization (HRU) and cost of HZ in patients with RA.

METHODS

Data Source

This study used de-identified data from Optum® Clinformatics® Data Mart (Optum CDM), an administrative claims database including commercial and Medicare Advantage with Medicare Part D (MAPD) health plan data, with a data period from October 1, 2015 to February 28, 2020. It captures approximately 15–19 million covered lives annually across all 50 states in the US.

This database included enrollment information as well as medical and pharmacy claims. Medical claims data included diagnosis and procedure codes, as well as information on the particular type and setting of the healthcare service performed by each provider. The place of service field was used to define the settings of care for each specific claim, which included outpatient (office visits, consultations, and visits at outpatient facilities, among others), inpatient (any claims that came from Optum confinement records), emergency department, and other settings of care (for example, skilled nursing facility, home care services, hospice, vision, and durable medical equipment use). Pharmacy claims data included medication dispensed (identified by national drug codes) as well as the days of supply, refills, and costs. Claims from medical and pharmacy benefits also included the dates of service.

As only existing de-identified data were used and no patients were contacted during the course of this study, informed consent was not applicable and Institutional Board Review was not required. These de-identified data complied with the requirements of the Health Insurance Portability and Accountability Act, and the study was conducted in accordance with the guiding principles of the Declaration of Helsinki.

Study Design

This retrospective, longitudinal cohort study included patients aged ≥ 18 years with RA who were divided into two cohorts: patients diagnosed with RA only (RA+/HZ−) and patients diagnosed with RA and HZ (RA+/HZ+). Patients were identified using International Classification of Diseases and Related Health Problems (10th Revision, Clinical Modification; ICD-10-CM) diagnosis codes, as well as National Drug Codes from pharmacy claims, based on previously validated claims algorithms [18–21].

Study Population

Patients with RA were identified using ICD-10-CM codes M05 and M06 (excluding M06.1 and M06.4). RA diagnosis was defined by at least two medical claims associated with a diagnosis code for RA at least 6 weeks apart, and at least one prescription for a disease-modifying anti-rheumatic drug (DMARD) for at least 3 months in the year following the first RA diagnosis.

HZ diagnosis was defined by at least one claim associated with ICD-10-CM B02 occurring on a day not associated with HZ vaccination. Notably, patients were excluded from the RA+/HZ+ cohort if their first HZ diagnosis was associated with other nervous system involvement (ICD-10-CM B02.2, potentially suggesting a prevalent case of PHN following a prior HZ infection).

HZ complication-specific ICD-10-CM diagnosis codes were also used to identify HZ-related complications following an initial HZ diagnosis in the RA+/HZ+ cohort, including PHN, HZO, disseminated HZ, and HZ-related

meningoencephalitis (Supplementary Table S1). This manuscript specifically discusses results for PHN and HZO as two of the most common complications of HZ [2]. Patients with PHN were identified using the ICD-10-CM code B02.2, or at least one claim associated with a HZ diagnosis ≥ 90 days after the initial HZ diagnosis, in addition to at least one claim for medication used to treat PHN, or for a pain intervention, on or within 30 days of such second HZ diagnosis (without evidence of use in the year prior). Patients with HZO were identified using the ICD-10-CM code B02.3, or at least one claim associated with a diagnosis of eye complications within 30 days of HZ diagnosis.

For the RA+/HZ+ cohort, the index date was defined as the date of the first claim with a HZ diagnosis. For the RA+/HZ− cohort, an index date was randomly assigned based on the distribution of time between the beginning of continuous enrollment and the index dates in the RA+/HZ+ cohort. This ensured that the distribution of pre-index eligibility for the RA+/HZ− cohort followed that of the RA+/HZ+ cohort, with respect to time from the start of continuous enrollment to index date. At least 12 months of continuous enrollment prior to and after the index date were required for both study cohorts (full study design presented in Fig. 1). Patients were excluded from both cohorts if they received a HZ vaccine, either recombinant zoster vaccine or zoster vaccine live, during the baseline period or on the index date, in an attempt to ensure that the cohorts were HZ vaccine-naïve. Patients who received a HZ vaccination post-index were included, as they may have received this to avoid recurrence of HZ. Therefore, the outcomes for these patients constituted part of the disease burden that the study aimed to evaluate.

Study Measures

Patient Baseline Characteristics

Baseline demographic and clinical characteristics of patients were assessed during the 12-month period prior to the index date ("baseline period"). Demographic characteristics included age, sex, geographic region within the US, and type of insurance plan (commercial or MAPD). Clinical characteristics included Charlson-Quan Comorbidity Index (CCI) score (modified to exclude rheumatologic disease), medications during the baseline period (assessed using pharmacy claims and procedure codes), selected immunosuppressive conditions (SOT, BMSCT, chemotherapy for malignancy, symptomatic HIV), and comorbidities potentially associated with HZ (assessed using diagnosis codes).

Healthcare Resource Utilization and Costs

The baseline period was followed by the "observation period", defined as the period between the index date and the end of data availability, lasting a minimum of 12 months. During the observation period, all-cause HRU and costs were measured for the RA+/HZ+ and RA+/HZ− cohorts over the first month (month 1), quarter (quarter 1), and year (year 1).

HRU included the frequency of inpatient stays, emergency department visits, outpatient visits, and services and encounters in other settings. HRU outcomes for month 1, quarter 1, and year 1 were reported as the mean number of HRU events per patient for the respective time horizons. Incidence rates (IRs) were calculated by dividing the number of encounters in the observation period by the patient-time observed. While these are referred to as IRs in the analysis, they represent count or frequency of events rather than singular incident events.

Healthcare costs included medical and pharmacy costs, which were adjusted to 2020 US dollars (USD) using the medical care component of the Consumer Price Index [22]. Medical costs were measured overall and for specific settings (inpatient, emergency department, outpatient, and other settings). Medical costs also encompassed medications administered in a medical setting coded with a procedure code (e.g., biologics for RA given by intravenous infusion), which were categorized by the setting in which the medication was administered and billed. Pharmacy costs were derived from the costs in pharmacy claims data covered under the patients' pharmacy benefit scheme. Total healthcare costs were measured as the sum of medical and pharmacy costs. All

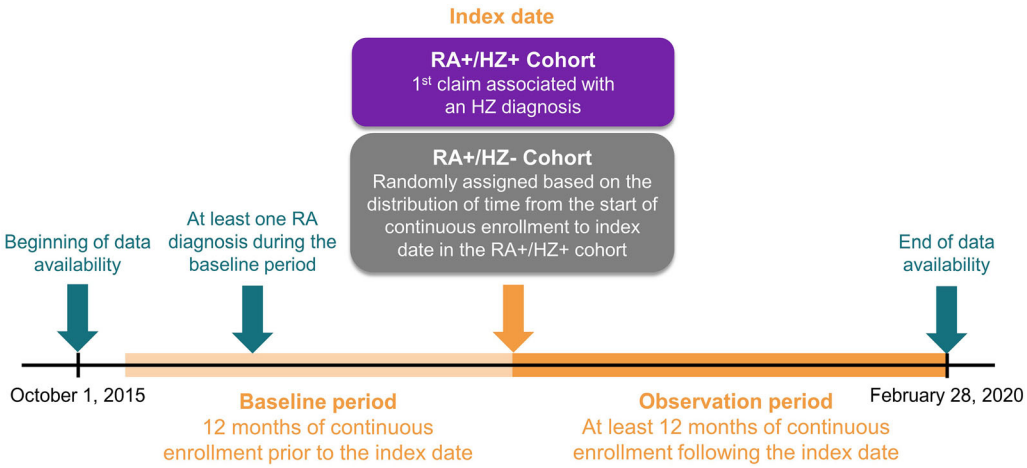


Fig. 1 Study design. During the baseline period, baseline characteristics were assessed along with clinical characteristics including modified Charlson-Quan Comorbidity Index and component conditions, comorbidities potentially associated with HZ, additional immunosuppressive conditions, use of RA-related medications prior to index date, surgeries, and all-cause healthcare costs (including medical service and pharmacy costs). During the observation period, HRU and costs were measured for the RA+/HZ+ cohort, RA+/HZ− cohort, and HZ-related complication costs were measured for patients within the RA+/HZ+ cohort. *HRU* healthcare resource utilization, *HZ* herpes zoster, *RA* rheumatoid arthritis

costs represented an estimate of the allowed amount, as opposed to paid or billed amounts.

Healthcare Resource Utilization and Costs Associated with HZ-Related Complications

HRU and medical costs associated with diagnoses of HZ-related complications on medical claims, including PHN and HZO, in the RA+/HZ+ cohort were also measured during the observation period and reported for year 1. These were measured for each setting and identified based on the relevant ICD-10-CM codes. Costs for HZ-related complications were adjusted to 2020 USD and were reported as mean costs across the full RA+/HZ+ cohort, and as mean costs for those with non-zero costs associated with these complications.

Statistical Analysis

All study measures, both baseline and follow-up, were reported using descriptive statistics. Statistical analyses were conducted using the statistical software SAS 9.4, SAS Studio and SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA).

Patient Baseline Characteristics

Baseline demographic and clinical characteristics for both cohorts were compared using standardized differences (the full formula for calculation can be found in the footnote of Table 1). Standardized differences of 20, 50, and 80% were considered small, medium, and large differences, respectively [23].

Healthcare Resource Utilization and Costs

Multivariable regression models were used to compare health resource utilization and costs outcomes, incorporating propensity score-based covariate adjustment and further inclusion of the full set of relevant patient baseline characteristics (which were also used in estimating the propensity scores). This doubly robust approach was employed to account for variables where there were baseline differences in the populations of meaningful magnitude or where variables were expected to be clinically relevant confounders, to limit bias in the assessment outcomes. Covariate adjustment using propensity scores is a typical application of the method and known to produce reliable results based on previous research [24, 25].

Propensity scores were calculated using logistic regression with HZ status as the dependent variable and relevant baseline characteristics as predictors. Patient baseline covariates included: age at index, sex, geographic region, insurance type, modified CCI, presence of any comorbidity potentially associated with HZ, presence of any additional immunosuppressive condition, RA-related medication prior to index date (use of RA therapies, alone or in combination; Table 1), and total baseline all-cause healthcare costs. All-cause total baseline costs were included as a covariate in both propensity score estimation as well in the final multivariable models, so that this key baseline measure was accounted for when comparing the utilization and cost outcomes between cohorts during the observation period. A similar approach was previously used to assess the economic burden of HZ among patients with chronic obstructive pulmonary disease (COPD) [26].

Following propensity score estimation, HRU was compared between cohorts using adjusted incidence rate ratios (IRRs). These adjusted IRRs and 95% confidence intervals (CIs) were calculated using generalized linear models with a negative binomial distribution and log link, adjusting for the propensity score (as a continuous variable) and its component predictors.

Healthcare costs were compared between cohorts using a two-part generalized linear model. The first part of the model involved modeling the probability of a patient incurring a non-zero cost, given cohort status and baseline patient characteristics. The second part involved predicting costs among patients who incurred positive costs in these data, using a generalized linear model with a gamma distribution and log link. The cost difference between cohorts was estimated by combining the probability from the first part with the predicted costs from the second part, adjusting for the propensity score (as a continuous variable) and its component predictors. CIs and *p* values were estimated from non-parametric bootstrap procedures with 499 replications.

The HRU and costs of HZ-related complications among the HZ+/RA+ cohort were summarized descriptively, and not compared between cohorts since there were no HZ-related costs among the RA+/HZ− cohort.

RESULTS

Study Population

During the study period, 118,630 patients were identified with a confirmed diagnosis of RA. After applying all study eligibility criteria, the final study population included 1866 patients in the RA+/HZ+ cohort and 38,846 patients in the RA+/HZ− cohort (Fig. 2).

Patient Baseline Characteristics

The baseline characteristics of the final study population are presented in Table 1. Across both cohorts, most patients were female (RA+/HZ+: 79.8%, RA+/HZ−: 76.0%). More than half of the patient population were aged ≥ 65 years (RA+/HZ+: 64.1%; RA+/HZ−: 59.2%). Correspondingly, the majority of patients had Medicare Advantage insurance (RA+/HZ+: 71.7%, RA+/HZ−: 67.4%), whereas the remaining patients were commercially insured.

Overall, the RA+/HZ+ cohort had a higher mean [SD] age compared with the RA+/HZ− cohort (68.3 [11.6] vs. 66.2 [12.7], respectively; standardized difference: 17.1%). Approximately 75% of patients in both cohorts used conventional DMARDs and around 30% used biologics, although more RA+/HZ+ patients used systemic glucocorticoids than RA+/HZ− patients (39.2 vs. 28.4%, standardized difference: 22.9%). The RA+/HZ+ cohort also had greater comorbidity burden compared with the RA+/HZ− cohort, as described by the CCI (1.3 [1.7] vs. 1.1 [1.6]). However, the standardized difference for this parameter (10.2%) was less than the threshold defining a small difference for this study (20%) [23].

Finally, during the baseline period, total annual healthcare costs were higher in the RA+/HZ+ cohort compared to the RA+/HZ− cohort ($52,625 [67,774] vs. $46,332 [65,480] per patient per year [PPPY]), though the standardized difference in baseline costs was 9.4%.

Table 1 Patient baseline demographic, clinical, and cost information

	RA+/HZ+ *N* = 1866	RA+/HZ− *N* = 38,846	Standardized difference (%)[1]
Age at index date, years, mean ± SD [median][2]	68.3 ± 11.6 [69.9]	66.2 ± 12.7 [68.2]	17.1
18–49, *n* (%)	129 (6.9)	4326 (11.1)	14.7
18–29, *n* (%)	2 (0.1)	332 (0.9)	10.8
30–39, *n* (%)	41 (2.2)	1135 (2.9)	4.6
40–49, *n* (%)	86 (4.6)	2859 (7.4)	11.6
50–64, *n* (%)	540 (28.9)	11,521 (29.7)	1.6
≥65, *n* (%)	1197 (64.1)	22,999 (59.2)	10.2
Sex, *n* (%)[3]			
Male	337 (20.2)	9325 (24.0)	9.2
Female	1489 (79.8)	29,521 (76.0)	9.2
Geographic region, *n* (%)[4]			
South	806 (43.2)	17,595 (45.3)	4.2
West	461 (24.7)	8943 (23.0)	3.9
Midwest	421 (22.6)	8633 (22.2)	0.8
Northeast	178 (9.5)	3655 (9.4)	0.4
Insurance type, *n* (%)			
Medicare advantage	1338 (71.7)	26,166 (67.4)	9.4
Commercial	528 (28.3)	12,680 (32.6)	9.4
Modified CCI, mean ± SD [median]	1.3 ± 1.7 [1.0]	1.1 ± 1.6 [0.0]	10.2
0, *n* (%)	855 (45.8)	19,698 (50.7)	9.8
1, *n* (%)	401 (21.5)	7846 (20.2)	3.2
2–4, *n* (%)	498 (26.7)	9526 (24.5)	5.0
≥ 5, *n* (%)	112 (6.0)	1776 (4.6)	6.4
Use of RA-related medications, *n* (%)[5]			
NSAIDs[6]	435 (23.3)	8063 (20.8)	6.2
Systemic steroids[6]	731 (39.2)	11,013 (28.4)	22.9
Category 2 medications: DMARDs[6]	1406 (75.3)	29,055 (74.8)	1.3
Category 3 medications: Biologics[7]	555 (29.7)	11,382 (29.3)	1.0
Category 5 medications: JAK inhibitors[8]	86 (4.6)	1011 (2.6)	10.8
RA-related medications prior to index date, *n* (%)			
Category 2 medications alone	623 (33.4)	15,673 (40.3)	14.4

Table 1 continued

	RA+/HZ+*N* = 1866	RA+/HZ−*N* = 38,846	Standardized difference (%)[1]
Category 3 or 5 with or without category 2 medications	400 (21.4)	8743 (22.5)	2.6
Systemic steroids with or without any of the above medications	731 (39.2)	11,013 (28.4)	22.9
Services accessed during baseline period, *n* (%)			
Inpatient visits[9]	354 (19.0)	5791 (14.9)	10.8
Emergency department visits	689 (36.9)	11,642 (30.0)	14.7
Outpatient visits	1866 (100.0)	38,839 (100.0)	1.9
Other[10]	1180 (63.2)	22,449 (57.8)	11.1
All-cause healthcare costs[11]			
Total healthcare costs, PPPY, 2020 USD, mean ± SD [median]	52,625 ± 67,774 [33,352]	46,332 ± 65,480 [24,248]	9.4

[1] For continuous variables, the standardized difference was calculated by dividing the absolute difference in means of the RA+/HZ+ vs. RA+/HZ− cohorts by the pooled standard deviation of both groups. The pooled standard deviation was the square root of the average of the squared standard deviations. For categorical variables with two levels, the standardized difference was calculated using the following equation where P1 was the respective proportion of participants in the RA+/HZ+ cohort, and P2 was the respective proportion of participants in the RA+/HZ− cohort: $\text{abs}(P1\text{-}P2)/\sqrt{p(1\text{-}p)}$, where p = (P1+P2)/2. Standardized differences of 20, 50, and 80% suggest small, medium, and large differences, respectively. [2] To ensure de-identification, patients' dates of birth were never earlier than 1930 in the data source; therefore, the maximum patient age as of the index date is 89. [3] One patient in RA+/HZ− had "unknown" sex and was imputed as "female" sex. [4] Twenty patients from the RA+/HZ− cohort were of unknown geographic region. [5] Medication categories were mutually exclusive and stratified. [6] The observation window of NSAIDs, 5-aminosalicylate, aminosalicylate, sulfasalazine, thiopurines, steroids, and conventional DMARDs, was 6 months prior to index date, and the medication duration had to cover the index date. [7] The observation window of biologics was defined as being 3 months immediately before the index date. For rituximab (Rituxan) or rituximab-abbs/rituximab-pvvr (Truxima) specifically, this was 6 months immediately before the index date. [8] The observation window for JAK inhibitors was defined as being 3 months before the index date. [9] The inpatient category includes the HRU associated with admission within the period of interest. [10] Other category HRU included durable medical equipment use, home health/hospice visits, services and supplies, and transportation services. [11] Costs were evaluated as the cost associated with all inpatient stays, outpatient visits, emergency department visits and all other visits, regardless of the associated diagnosis or procedure. *CCI* Charlson-Quan Comorbidity Index, *DMARD* disease-modifying anti-rheumatic drug, *HRU* healthcare resource utilization, *HZ* herpes zoster, *JAK* Janus kinase, *NSAID* non-steroidal anti-inflammatory drug, *PPPY* per patient per year, *RA* rheumatoid arthritis, *SD* standard deviation, *USD* US dollar.

Healthcare Resource Utilization

Unadjusted IRs of HRU were higher in the RA+/HZ+ than the RA+/HZ− cohort across all timepoints (month 1, quarter 1, and year 1) during the first year of the observation period (Table 2). At year 1, unadjusted IRs for inpatient and emergency department visits for the RA+/HZ+ cohort were 0.3 and 1.0 visits per year, respectively, compared with the RA+/HZ− cohort which had 0.2 and 0.8 visits per year, respectively.

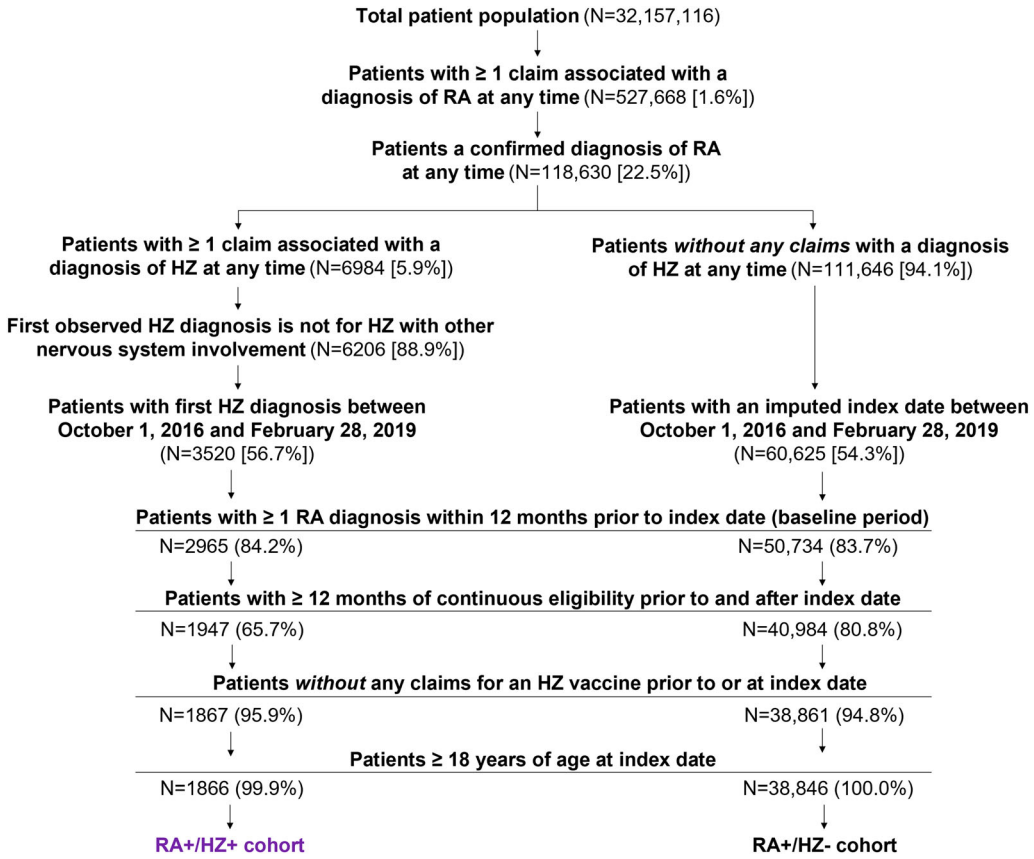


Fig. 2 Study sample selection. Patients were identified from medical and pharmacy claims in the Optum Clinformatics Data Mart Database, a large de-identified US insurance database, between October 1, 2015 and February 28, 2020. *HZ* herpes zoster, *RA* rheumatoid arthritis, *US* United States

Adjusted IRRs comparing the number of encounters in the RA+/HZ+ to the RA+/HZ− cohort were highest at month 1 after the index date and decreased over time across quarter 1 and year 1 for all HRU parameters (Fig. 3). For example, at month 1, inpatient admissions and emergency department visits occurred 3.43 (95% CI: 2.77; 4.23) and 3.66 (95% CI: 3.04; 4.40) times more frequently in the RA+/HZ+ than in the RA+/HZ− cohort, respectively. In comparison, at year 1, inpatient and emergency department admissions occurred 1.16 (95% CI: 1.04; 1.30) and 1.34 (95% CI: 1.21; 1.47) times more frequently, respectively.

Lower adjusted IRRs were observed for outpatient visits across timepoints (ranging from 1.11–1.64) relative to inpatient admissions and emergency department visits. However, IRRs were >1 overall, indicating higher outpatient HRU among the RA+/HZ+ than RA+/HZ− group. Attenuating utilization over time was also observed, similar to other types of HRU.

Costs

Mean unadjusted total costs per patient were also higher among the RA+/HZ+ cohort than the RA+/HZ− at every time point during the first year of the observation period (Supplementary Table S2).

At month 1, quarter 1, and year 1, mean (SD) adjusted total cost differences comparing the costs between the RA+/HZ+ and RA+/HZ− cohorts were $3404 (95% CI: $2089; $4779), $3080 (95% CI: $1347; $4807) and $3325 (95% CI: −$58; $7345), respectively (Fig. 4). Differences were driven by medical costs, particularly hospitalization costs, both of which were higher

Table 2 Unadjusted HRU across all time periods during the observation period

RA+/HZ+ N = 1866 RA+/HZ− N = 38,846	Month 1		Quarter 1		Year 1	
	RA+/HZ+	RA+/HZ-	RA+/HZ+	RA+/HZ-	RA+/HZ+	RA+/HZ-
HRU, *n* (%)						
Inpatient visits[1]	118 (6.3)	640 (1.6)	178 (9.5)	1886 (4.9)	405 (21.7)	6301 (16.2)
Emergency department visits	308 (16.5)	1722 (4.4)	430 (23.0)	4243 (10.9)	770 (41.3)	11,810 (30.4)
Outpatient visits	1813 (97.2)	27,921 (71.9)	1862 (99.8)	36,736 (94.6)	1866 (100.0)	38,508 (99.1)
Other[2]	367 (19.7)	6169 (15.9)	628 (33.7)	11,365 (29.3)	1182 (63.3)	22,809 (58.7)
Mean number of visits per time period[3], average per patient						
Inpatient visits[1]	0.07	0.02	0.11	0.06	0.33	0.24
Emergency department visits	0.22	0.06	0.37	0.19	1.03	0.77
Outpatient visits	3.11	1.84	7.46	5.51	26.33	22.22
Other[2]	0.32	0.28	0.91	0.83	3.83	3.36

The observation period was defined as the time between the index date and the end of continuous eligibility or end of data availability, whichever occurred first. [1] The inpatient category reflects HRU associated with admissions within the period of interest. [2] Other category included skilled nursing facilities, home care services, hospice, vision care, and durable medical equipment use. [3] Incidence rate was calculated by dividing the number of encounters over the observation period by the patient-time observed, and was reported on a PPPY basis for the first year of the observation period. For the other time horizons, the average number of HRU events per patient was described. *HRU* healthcare resource utilization, *HZ* herpes zoster, *PPPY* per patient per year, *RA* rheumatoid arthritis

among the RA+/HZ+ than RA+/HZ− cohort throughout the observation period, including at year 1. Pharmacy costs did not differ between cohorts in adjusted analyses, except at quarter 1 (−$317; 95% CI: −$561; −$51).

Healthcare Resource Utilization and Costs Associated with HZ-Related Complications

At year 1, 260 (13.9%) patients in the RA+/HZ+ cohort had visits related to PHN, 165 (8.8%) had visits related to HZO, 31 (1.7%) had visits related to disseminated HZ, and 5 (0.3%) had visits related to meningoencephalitis (Supplementary Table S3).

As a proportionately small number of RA+/HZ+ patients had complications, the unadjusted complication-related costs appeared to be low when averaged across the whole RA+/HZ+ cohort (Supplementary Table S4). However, those with complications were noted to have high unadjusted costs (Supplementary Table S5). For example, in the RA+/HZ+ cohort, among the 259 (13.9%) and 165 (8.8%) patients who incurred costs associated with PHN and HZO at year 1, the mean (SD) unadjusted total medical costs associated with these conditions were $3773 ($14,806) and $4226 ($19,179), respectively.

The majority of patients with these complications incurred complication-specific outpatient costs (mean unadjusted total outpatient costs [SD] for PHN: $1193 [$5542], n = 250; HZO: $599 [$1355], n = 117). Despite being associated with a relatively small proportion of patients, unadjusted complication-specific inpatient costs were noted to be particularly high among patients who incurred these costs (mean unadjusted total inpatient costs [SD] for PHN: $28,993 [$38,312], n = 22; HZO: $29,719 [$48,355], n = 20).

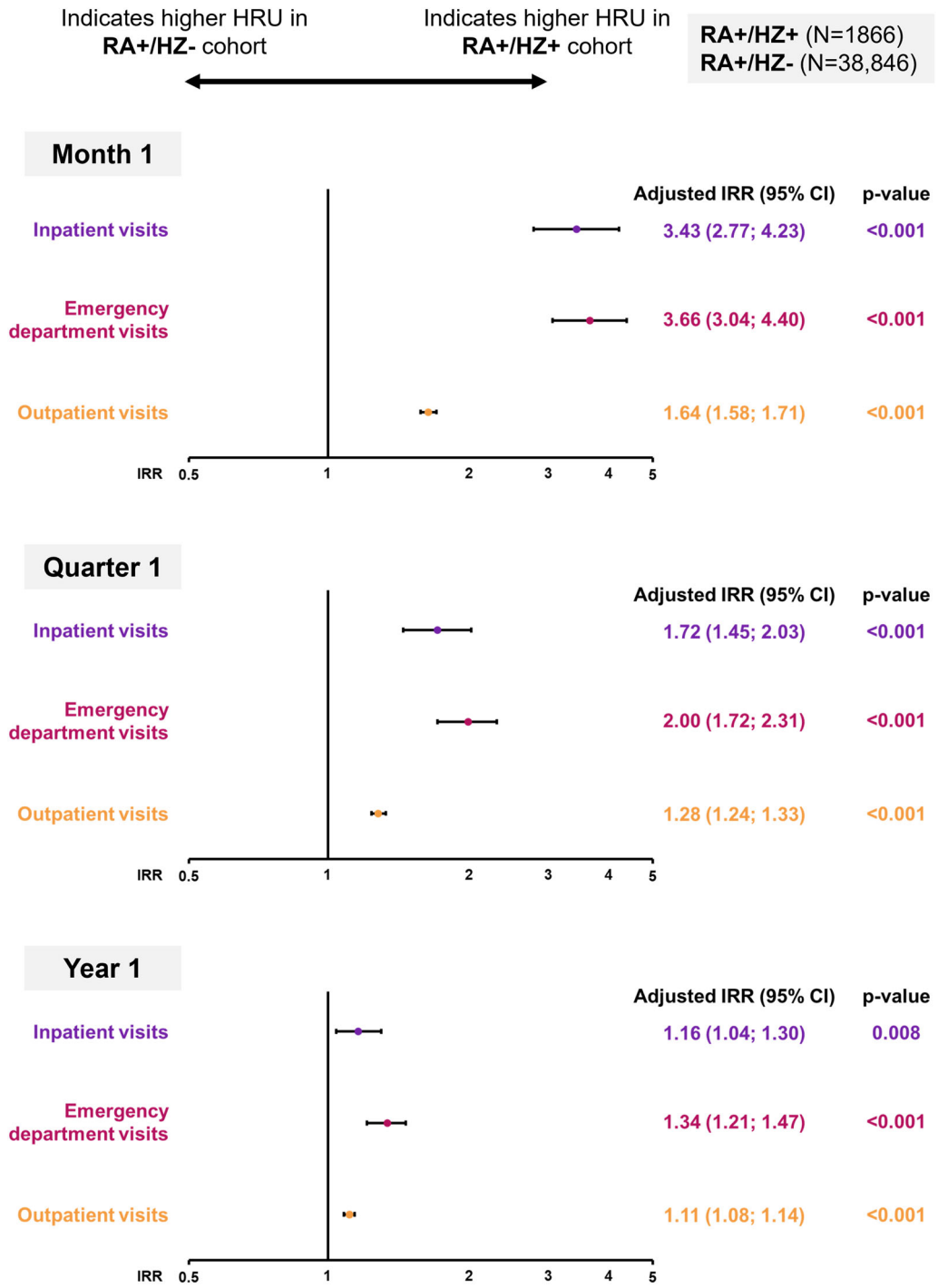
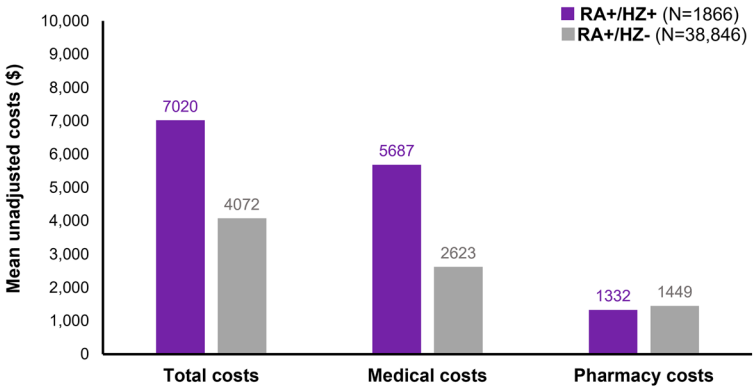


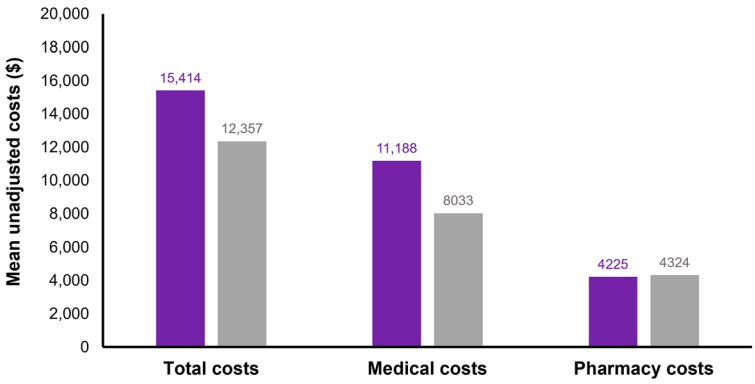
Fig. 3 Adjusted IRRs for HRU at month 1, quarter 1, and year 1 in patients with RA and HZ compared to patients with RA and without HZ. IRRs were used to compare HRU between the RA+/HZ+ and RA+/HZ− cohorts at month 1, quarter 1, and year 1. IRRs were calculated using the PROC GENMOD procedure for generalized linear models assuming a negative binomial distribution and log link, accounting for the propensity score of being in the RA+/HZ+ cohort and relevant baseline characteristics. *CI* confidence interval, *HRU* healthcare resource utilization, *HZ* herpes zoster, *IRR* incidence rate ratio, *RA* rheumatoid arthritis.

Month 1



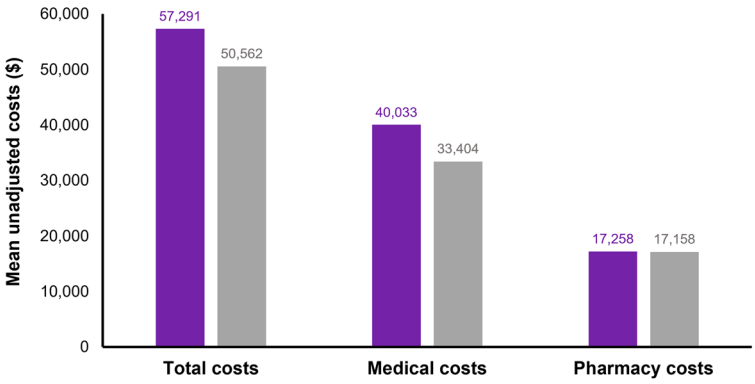
	Total costs	Medical costs	Pharmacy costs
Unadjusted cost differences	$2948	$3064	$-117
Adjusted cost differences (95% CI)	$3404 ($2089; $4779)	$2677 ($1692; $3670)	$-82 ($-182; $35)

Quarter 1



	Total costs	Medical costs	Pharmacy costs
Unadjusted cost differences	$3057	$3155	$-99
Adjusted cost differences (95% CI)	$3080 ($1347; $4807)	$2657 ($1086; $4065)	$-317 ($-561; $-51)

Year 1



	Total costs	Medical costs	Pharmacy costs
Unadjusted cost differences	$6729	$6629	$100
Adjusted cost differences (95% CI)	$3325 ($-58; $7345)	$3428 ($446; $6781)	$-833 ($-1846; $386)

◀**Fig. 4** Mean unadjusted costs and adjusted cost differences at month 1, quarter 1, and year 1 in patients with RA and HZ compared to patients with RA and without HZ. Unadjusted cost differences are presented alongside adjusted cost differences and their 95% CI values. Adjusted cost differences and 95% CI values were estimated from non-parametric bootstrap procedures with 499 replications. All costs were adjusted to 2020 USD using the medical care component of the Consumer Price Index; data reflect average cost per patient within a given time period (per month, per quarter, or per year). *CI* confidence interval, *HZ* herpes zoster, *RA* rheumatoid arthritis, *USD* United States dollars

DISCUSSION

To our knowledge, this study is the first to estimate the incremental HRU and cost burden posed by HZ in patients with RA in the US.

Overall, HRU was higher among the RA+/HZ+ cohort compared to the RA+/HZ− cohort at all timepoints even after adjusting for baseline characteristics. The greatest magnitude of difference in HRU was observed shortly following initial HZ diagnosis. Differences were more pronounced for acute forms of HRU, such as hospitalization and emergency department visits, compared with outpatient utilization, which may reflect the high relative impact of incremental acute HRU. For example, at month 1, hospitalization and emergency department visits among the RA+/HZ+ cohort occurred at more than 3 times the rate compared with RA+/HZ− cohort.

Differences in HRU were also noted to be front-loaded in time before attenuating over the study period. Compared with month 1, adjusted IRRs across all HRU categories became less prominent at quarter 1 and year 1. This was expected, given that most RA patients in the study did not have long-term sequelae after an episode of HZ. Furthermore, it is expected that a significant proportion of HRU associated with HZ would occur shortly after diagnosis and during the acute phase of disease. As such, this HRU may compound on routine visits for the management of RA.

Reflecting differences in HRU, total unadjusted costs were also higher among the HZ+/RA+ cohort at all timepoints during the observation period. Increased costs were mainly associated with hospitalization and emergency department visits, indicating that management of acute episodes of HZ are expected to be the main cost drivers. Conversely, no differences in pharmacy costs were noted except at quarter 1. This may be attributable to the relatively low cost of drug treatment for HZ, which would primarily comprise of generic antivirals and medication for pain management [2, 27].

Though they constituted a minority of this population, patients within the RA+/HZ+ cohort who experienced complications of PHN or HZO had high complication-specific costs. Patients who had an inpatient admission associated with PHN or HZO incurred particularly high costs, a pattern observed in previous research [5].

These results therefore highlight the heavy burden among RA patients with HZ, and the added burden among those with HZ-related complications, which are congruent with patterns of HRU and costs associated with HZ among other patient populations with immunocompromising conditions. For example, a study conducted using data from 2005–2009 which included patients with SOT, HIV, and BMSCT similarly reported greater HRU among those with HZ than those without HZ, as well as similar cost differences (adjusted to 2014 USD) to our current study [11]. These cost differences were also mainly incurred during the first 90 days following diagnosis, ranging from $2549 among cancer patients aged 18–64 years, to $3108 among cancer patients aged > 64 years. For BMSCT patients, a higher cost difference of $13,332 was observed in the first quarter following index date, which was expected as this population experiences a particularly high degree of immunosuppression.

A similar pattern of higher healthcare costs being incurred in the time shortly following HZ diagnosis has been observed among other patient groups with non-immunocompromising or autoimmune conditions. For example, a study which utilized similar methodology for adjusting costs found that patients with COPD and HZ incurred consistently higher costs than COPD patients without HZ [26]. The most

prominent cost differences were similarly observed within the first month after diagnosis, providing further confidence in this study's findings.

These findings may point towards HZ prevention strategies to avoid the economic and clinical disease burden among the immunocompromised population. Vaccination may be one such strategy; a previous study demonstrated that vaccination against HZ is a cost-effective approach to preventing the medical and economic burden associated with HZ in older adults in the US [28]. Data from this study may therefore also support recommendations by the Advisory Committee on Immunization Practices to vaccinate immunodeficient or immunosuppressed individuals aged $\geq$ 19 years to prevent HZ and its complications [29], including patients with well-controlled autoimmune and inflammatory disease as described in clinical guidance from the Centers for Disease Control and Prevention [30]. Furthermore, recent guidelines by the American College of Rheumatology strongly recommend the recombinant zoster vaccine for patients aged $>$ 18 years with rheumatic and musculoskeletal diseases who are taking immunosuppressive medication [31].

Strengths and Limitations

Overall, this study contributes key data which help establish the burden of HZ within patients with RA, working towards filling in a gap in current literature. A strength of this study is the doubly robust approach used for the adjusted analyses, which helped account for differences in baseline characteristics between RA patients with HZ compared to those without. Furthermore, a large database was used, which encompassed a diverse sample of commercial and Medicare Advantage enrollees. As claims generally capture a complete record of services covered by insurance providers, cost estimates and HRU estimates are likely to be relatively reliable. A more nuanced understanding of HRU and cost patterns in this patient population was also attained by measuring outcomes over various time horizons. Potential future avenues of research could include a comparison between vaccinated and non-vaccinated patients with RA to contextualize the impact of vaccination on the burden of HZ among the RA patient population.

One potential limitation of the data source is that claims databases lack detailed clinical information on patients. As administrative claims data are generated primarily for the payment of health services delivered by healthcare professionals and facilities and not for research, this prevented more detailed characterization of disease (including severity, progression, patient-reported outcomes [such as HZ-related pain], and quality of life). Without these details about the patient population in the study, it is more challenging to describe how representative the sample is, and to perform adjustment for any differences that were not captured among variables available in the claims from this study. This could therefore lead to confounding that may not have been completely adjusted for in the analysis (e.g., clinical severity of RA). However, the study included surrogate measures for disease severity (such as medication therapy and comorbidity burden) in an attempt to account for this limitation of the data source.

This study also employed a conservative identification approach by excluding patients from the RA+/HZ+ cohort if their first HZ diagnosis was associated with other nervous system involvement (ICD-10-CM B02.2x). This was made on the assumption that this would likely represent a prevalent case of PHN following a prior HZ infection, given that PHN is typically a complication preceded by an initial HZ diagnosis a few months earlier [30]. It is important to acknowledge that this approach may be limited by misclassification, due to coding imprecision in these claims data; for example, a PHN diagnosis representing incident HZ might be miscoding intended to represent more severe disease. However, it is unclear how common or likely this scenario is. Furthermore, some of these excluded cases (approximately 11% of patients [N = 778] with $\geq$ 1 claim associated with a diagnosis of HZ at any time) may have actually been more severe incident cases of HZ with higher costs, though such exclusion

would bias findings of the study toward the null.

It may also be noted that the medications used to identify PHN are not necessarily specific to PHN and could be used for RA. As such, PHN-specific costs and complication-associated costs as a whole may have been overestimated. This represents an inherent challenge in associating medication costs in claims data directly with a particular diagnosis or condition, whether it may be solely related to PHN, RA, or both concurrently. Nevertheless, this approach was taken to capture a range of different costs that may be associated with HZ in patients with RA, providing additional insights into the full economic burden of HZ-related complications.

Another potential limitation is that patients were required to have at least 12 months continuous enrollment following the index date. This may have inherently biased the data toward a healthier population of patients, as those who died during this period – potentially due to severe but rare complications or sequalae of HZ – would have been excluded. Furthermore, as patients with HZ may experience a prodromal phase which typically precedes diagnosis of HZ [2], some HZ-related HRU and costs may not be captured if they occurred before the index date.

In addition, although patients were excluded if they received an HZ vaccine any time before or on the index date, the period prior to the index that is available in the claims data may not wholly encompass the patient's history. Therefore, these patients may not necessarily be vaccine naïve.

Finally, results may not necessarily be generalizable to all adults with RA. While a large, diverse sample of patients were captured from commercial and Medicare Advantage enrollees, data may not be generalizable to patients with other types of insurance coverage (such as Medicaid or Medicare Fee-for-Service) or those without insurance at all.

CONCLUSIONS

In conclusion, these findings demonstrate the greater economic burden among individuals with RA and HZ compared to those with RA who do not develop HZ, highlighting a significant healthcare need in this population. Hospitalization and emergency department visits were notable settings of care associated with HZ burden in this population. These results suggest that the RA patient population could potentially benefit from HZ prevention strategies, which may help to avoid the incremental economic burden of HZ, such as HZ vaccination.

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Compliance with Ethics Guidelines. As only existing de-identified data were used and no patients were contacted during the course of this study, informed consent was not applicable and Institutional Board Review was not required. These de-identified data complied with the requirements of the Health Insurance Portability and Accountability Act, and the study was conducted in accordance with the guiding principles of the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as they are licensed by a commercial entity in the United States. Authors were granted permission to use the datasets for the current study.

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