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ORIGINAL RESEARCH

Herpes Zoster Risk Among US Cancer Patients Following Initiation of Immunosuppressive Therapy

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Purpose: Cancer and immunosuppressive medications used for its treatment increase the risk for herpes zoster (HZ) among adults. This study described the incidence of HZ and its complications among United States (US) adults with specific solid tumors and hematological malignancies following initiation of immunosuppressive therapy.

Patients and Methods: This retrospective cohort study used administrative claims data from October 2015 to December 2022 and included US adults with ≥1 immunosuppressive medication claim, ≥12 months continuous enrollment (baseline) prior to the first immunosuppressive medication claim, a cancer diagnosis, and no HZ diagnosis or vaccination in the baseline period. HZ incidence rates (IRs) were calculated as the number of new HZ cases per 1000 person-years at risk, stratified by cancer type and medication class. The proportions of patients with HZ-related complications such as postherpetic neuralgia, herpes zoster ophthalmicus, disseminated HZ, and HZ-related meningoencephalitis were described. A time-dependent Cox proportional hazards regression estimated adjusted hazard ratios, controlling for patient age, sex, race and ethnicity, comorbidities, prior healthcare utilization, insurance type, region, and baseline immunosuppressive medication use.

Results: The overall IRs of new HZ cases in patients with a solid tumor or a hematological malignancy were 20.9 (95% confidence interval [CI]: 20.33–21.52) and 31.1 (95% CI: 29.64–32.52) per 1,000 person-years, respectively. HZ IR was highest in patients with non-Hodgkin lymphoma (35.4, 95% CI: 33.05–37.77) or chronic lymphocytic leukemia (35.1, 95% CI: 31.24–39.24). By medication class, the highest HZ IRs were associated with mycophenolic acid, azathioprine, and oral glucocorticoids. In adjusted analyses, patients were more likely to develop HZ during periods of immunosuppressive medication use versus periods without (adjusted hazards ratio [95% CI]: 3.2 [3.01–3.39] for solid tumor, 3.2 [2.89–3.57] for hematological malignancy).

Conclusion: HZ incidence among US adults with solid tumors and hematological malignancies following immunosuppressive therapy initiation was high, reinforcing the need to prioritize HZ vaccination in these populations.

Plain Language Summary:

Why was the study done?

Adults with cancer have a higher risk of developing herpes zoster (HZ) compared to the general population, due to both cancer and its treatments. The risk of HZ in adults by cancer type and medication class has not yet been comprehensively examined.

What did the researchers do and find?

This study estimated HZ incidence among United States adults with cancer following immunosuppressive therapy initiation. This study found that HZ incidence is particularly high in patients with solid tumors or hematological malignancies in the period following immunosuppressive medication initiation. Moreover, patients consistently on immunosuppressive therapy were more likely to develop HZ compared to patients with less consistent use of immunosuppressive medications. We identified mycophenolic acid, azathioprine, and oral glucocorticoids as medications associated with higher rates of HZ incidence.

What do these results mean?

The findings provide oncologists and hematologists with information about the risk of HZ in patients with different cancer types during periods of immunosuppressive medication use. This may also inform decision makers about the need for HZ vaccination in patients at increased risk for HZ due to both their health condition and treatment. Finally, this may provide guidance to providers by linking the need for HZ prevention with specific classes of medications, irrespective of their connection to cancer therapy.

Keywords: herpes zoster, incidence, immunosuppression, solid tumor, hematological malignancy

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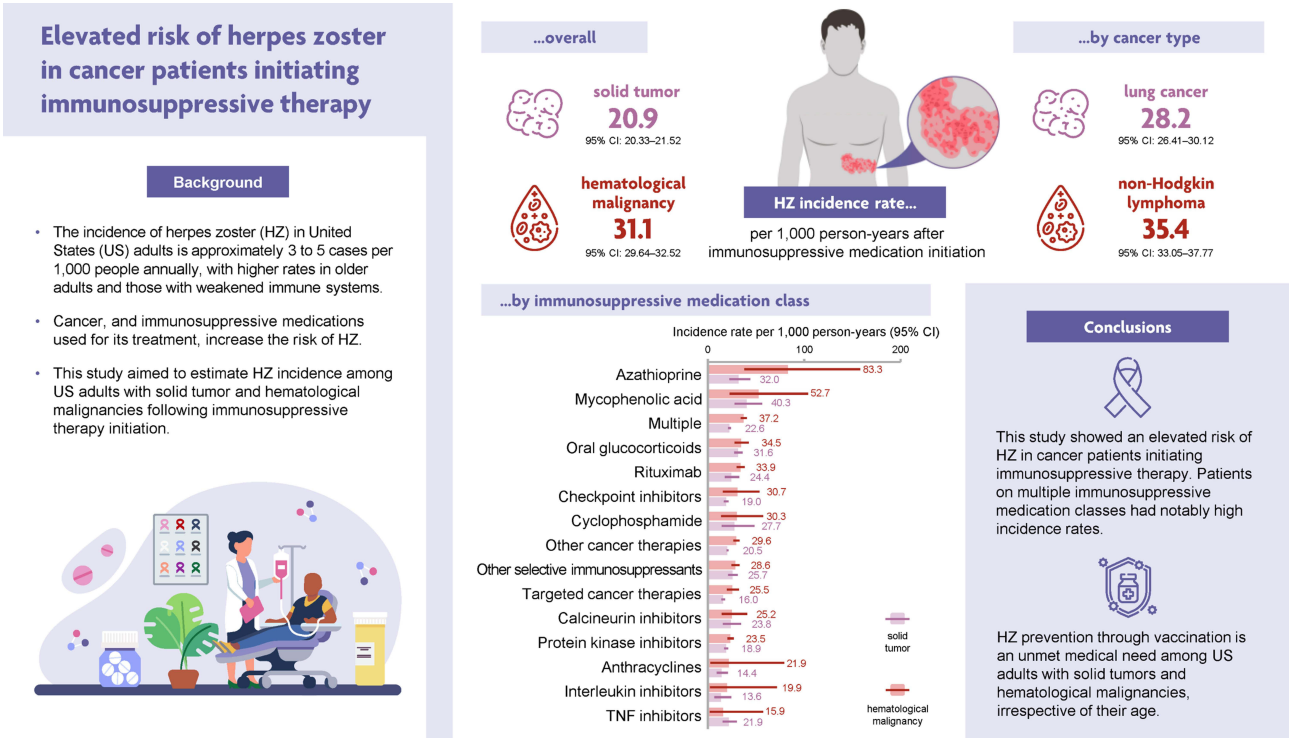
Graphical Abstract



Introduction

Herpes zoster (HZ), a condition which manifests primarily with a painful rash, is due to the reactivation of the varicella-zoster virus contracted earlier in life.[1–3] In the United States (US), nearly 1 in 3 individuals will develop HZ in their lifetime, amounting to 1 million cases each year.[1,2] In the immunocompetent adult US population, HZ incidence rates increase with age, ranging from 0.9 per 1,000 person-years (PY) in individuals aged ≤19 years to 12.8 per 1,000 PY in individuals aged ≥80 years.[4] HZ complications include postherpetic neuralgia (PHN), a chronic pain that may last for months to years.[5] Other complications associated with HZ include bacterial superinfection, scarring, nerve palsy, visual loss or disseminated disease in herpes zoster ophthalmicus (HZO), and meningoencephalitis.[3,6] Complications are more frequent and severe in immunocompromised individuals.[6–8]

Risk factors for HZ include age ≥50 years, female sex, family history of HZ, and immunocompromising conditions such as autoimmune disease, systemic lupus erythematosus, human immunodeficiency virus infection, solid organ transplant, cancer, and bone marrow or stem cell transplant.[6,9,10] Previous findings show that patients with transplantation or cancer had the highest risk of HZ among 21 underlying conditions identified as potential HZ risk factors, with odds ratios (ORs) of 4.5 (95% confidence interval [CI]: 1.9–10.7) and 2.4 (95% CI: 1.91–3.07), respectively, compared to individuals without these conditions.[10] Compared with HZ incidence rates in the general US population, age- and sex-standardized HZ rates were 4.8 and 1.9 times higher in patients with hematological malignancies or solid tumors, respectively. In patients with either cancer types, HZ risk also increased with the level of immunosuppression, defined based on the treatment type (specific chemotherapy agents and/or corticosteroids), the concurrence or recency of treatment, and the type of hematological malignancy, if applicable.[8] Additionally, specific to chemotherapy, a retrospective claims study found that the adjusted HZ incidence rate in patients with solid tumors receiving chemotherapy was 13.8 per 1,000 PY.[11] The risk of HZ also increases among patients with immunosuppressive

treatments for immune-mediated diseases,[12] specifically the use of systemic corticosteroids, tumor necrosis factor (TNF)-α inhibitors, and disease-modifying antirheumatic drugs.[12–14]

However, in general, there is limited evidence examining HZ incidence in adults by solid cancer or hematological malignancy type while considering immunocompromised status due to both the underlying condition and initiation of various immunosuppressive therapies. Data on the risk of HZ by cancer type and medication class used can help healthcare providers and decision makers understand the burden of HZ in patients with solid tumors or hematological malignancies who initiate various immunosuppressive therapies. Considering this, the current study aimed to describe the incidence of HZ and its complications among US adults with cancer initiating immunosuppressive medications overall and by periods of immunosuppression and non-immunosuppression, thus presenting a comprehensive, cross-cancer evaluation of disease risk associated with treatment initiation across the full spectrum of immunosuppressive therapies used in cancer care.

Materials and Methods

Study Design and Setting

This was a retrospective cohort study (GSK study identifier: VEO-000613) of US adults with cancer initiating immunosuppressive therapy using commercial and Medicare Advantage with Part D (MAPD) administrative claims from the Optum Research Database between October 1, 2015, and December 31, 2022. The study was conducted as a part of a broader analysis that evaluated the impact of immunosuppressive therapies on the incidence of HZ. This manuscript focuses on the incidence of HZ and the frequency of HZ-related complications among patients with different cancers undergoing immunosuppressive therapy.

Patient Population

Patients with ≥1 medical or pharmacy claim for a fill or administration of an immunosuppressive medication were included in the study, the initial filling of which served as the index date. In addition, patients had to be ≥18 years old as of the index date, have continuous enrollment in medical and pharmacy benefits for at least 12 months before the index date (baseline period), and have ≥2 non-diagnostic claims for a primary solid tumor or hematological malignancy on separate days in the baseline period. Patients were excluded if they had ≥1 medical claim for an HZ diagnosis during the baseline period, ≥1 medical or pharmacy claim for HZ immunization up to 5 years prior to the index date, evidence of pregnancy during the baseline period, or missing demographic information (eg, age, sex, or geographic region). An overview of the study periods and measured variables is provided in Figure S1.

Exposures

The medication classes included interleukin inhibitors, Janus kinase inhibitors, TNF-α inhibitors, other selective immunosuppressants, azathioprine, calcineurin inhibitors, mycophenolic acid, anthracyclines, checkpoint inhibitors, cyclophosphamide, protein kinase inhibitors, other cancer therapies, rituximab, targeted cancer therapies, and oral glucocorticoids. The complete list of medications included in the study is provided in Table S1.[15,16] Oral glucocorticoids included only chronic high dose oral systemic corticosteroids use (≥20 mg/day prednisone equivalence for ≥56 days of use during any 70-day period) from pharmacy claims.

The index date, and primary exposure, was based on the first fill or administration of an included immunosuppressive therapy, which was based on dispensing information (ie, days supply for fills/administrations) available in claims. Patients were considered exposed from the claim date through the duration of the supply provided on the pharmacy claim (2 weeks were added to the days' supply to account for gaps in coverage), or for a predetermined period based on the dosing schedule of the drug for medical claims.[17,18] Periods of immunosuppression were defined as the days on which patients had coverage for an active prescription fill (based on days supply) or administration of immunosuppressive medication, based on the dispensing information recorded in claims. In addition to this, periods of non-immunosuppression were defined as the days outside these treatment windows, when no active immunosuppressive therapy was documented. Several time-varying measures were also included in

the study: 1) use of any immunosuppressive therapy (yes/no) on each day of follow-up; 2) number of immunosuppressive medication classes (0, 1, ≥2) on each day of follow-up; and 3) use of index medication class (yes/no) on each day of follow-up. Patients were followed for a variable period after the index date until the earlier of an HZ diagnosis, HZ vaccination, pregnancy, disenrollment from the health plan, death, or end of the study period.

Study Data

The Optum Research Database is an extensive repository of US healthcare data that includes fully processed medical and pharmacy claims, along with linked enrollment information for commercial enrollees and MAPD beneficiaries. It encompasses data on over 73 million lives, accounting for approximately 8% of the US commercial enrollee population and 18% of the Medicare Advantage population. Medical claims or encounter data were collected from all available healthcare sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for all types of provided services. Medical claims and coding conform to insurance industry standards and include several procedure codes. Pharmacy claims data included drug name, dosage form, drug strength, fill/administration date, and days of supply.

Available socioeconomic characteristics linked to the administrative claims data and used to support analytics included household income category, household net worth category, and urban or rural residency. Clinical characteristics included the Quan-Charlson comorbidity score (CCI),[19,20] Agency for Healthcare Research and Quality (AHRQ) comorbid conditions,[21] immunocompromising and autoimmune conditions (including cancer), and select individual comorbid conditions. Patient characteristics included age, sex, race and ethnicity, insurance type, education level, geographic state, and region.

Outcomes

HZ cases were identified based on a previously validated diagnosis code for HZ (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10] code: B02).[22] Among patients with a diagnosis of HZ, the proportion with HZ-related complications on or after the HZ diagnosis date were identified using ICD-10 codes B02.0–B02.9, consistent with previous studies.[23–26] PHN was defined as having either: 1) ≥1 medical claim with an HZ diagnosis with other nervous system involvement; or 2) ≥1 medical claim with an HZ diagnosis ≥90 days after the date of the first HZ diagnosis and ≥1 medical or pharmacy claim for a medication to treat PHN or for a pain intervention on or within 30 days of this HZ diagnosis, with no evidence of use during the baseline period. HZO cases needed ≥1 medical claim with a diagnosis for HZO or ≥1 medical claim with a diagnosis for eye complications on or within 30 days after the date of the first HZ diagnosis, including unspecified chorioretinitis, unspecified iridocyclitis, blindness and low vision, keratitis, scleritis, episcleritis, and mydriasis. Disseminated HZ was defined as ≥1 medical claim with a diagnosis for disseminated HZ on or within 30 days after the date of the first HZ diagnosis. HZ-related meningoencephalitis was defined as ≥1 medical claim with a diagnosis for HZ encephalitis or HZ meningitis in the hospital setting on or within 6 months after the date of the first HZ diagnosis.

Analysis

Patient demographic and clinical characteristics were described separately for those with either a solid tumor cancer or hematological malignancy. Numbers and percentages were provided for categorical variables while means, with standard deviations (SDs), and medians, with interquartile ranges (IQRs), were provided for continuous variables.

HZ incidence was estimated where the numerator corresponded to the number of HZ cases that occurred following the index date, and the denominator was the time in days from the index date to the earlier of HZ diagnosis, HZ vaccination, evidence of pregnancy, disenrollment from the health plan, death, or the end of the study period. HZ incidence rates were presented as the number of new HZ cases per 1,000 PY at risk. Results were stratified by demographic and clinical characteristics, with point estimates and 95% CI, and provided for each cancer category and subtype.

Complications related to HZ were reported for each cancer cohort (ie, solid tumor, hematological malignancy) as numbers and percentages among patients with a diagnosis for HZ and with sufficient continuous enrollment (6 months for PHN and HZ-related meningoencephalitis or 30 days for HZO and disseminated HZ).

Time-dependent Cox regression compared the adjusted hazard of HZ between periods of immunosuppression and non-immunosuppression among patients initiating immunosuppressive medication, as defined by time-varying immunosuppressive therapy use in the follow-up period. Separate models were used for solid tumors and hematological malignancies. The models controlled for patient age, race and ethnicity, insurance type, region, CCI, AHRQ comorbidities, healthcare utilization, and baseline immunosuppressive medication use.

Results

Patient Population

Following selection, 155,913 adult patients with a solid tumor cancer and 34,331 patients with a hematological malignancy were identified (Figure S2). The most common solid tumor cancers were breast (21.4%), lung (18.1%), and colorectal (13.0%) (Table 1). Among the population with hematological malignancies, the most common types were non-Hodgkin lymphoma (42.6%), multiple myeloma (20.5%), and chronic lymphocytic leukemia (14.0%).

The solid tumor population was 54.5% female and on average 67.3 years old (SD: 12.4), while the hematological malignancy group was mostly male (55.8%) and had a similar mean age (68.4 years, SD: 13.8) (Table 1). Both groups were mostly composed of non-Hispanic White individuals.

The most prevalent specific immunosuppressive medication classes at index were checkpoint inhibitors (7.5%) and protein kinase inhibitors (6.6%) for the solid tumor population, and protein kinase inhibitors (13.7%) and rituximab (11.9%) in patients with hematological malignancies. However, 19.7% and 26.0% of patients were on multiple therapies at index in the solid tumor and hematological malignancy cohorts, respectively (Table 1).

Table 1 Demographic and Clinical Characteristics

Demographics	**Solid Tumor (N = 155,913)**	**Hematological Malignancy (N = 34,331)**
Mean age, years (SD)	67.3 (12.4)	68.4 (13.8)
Median age, years (Q1–Q3)	69.0 (60.0–76.0)	71.0 (61.0–78.0)
Age group, years (n, %)		
18–29	908 (0.6)	677 (2.0)
30–39	3,468 (2.2)	906 (2.6)
40–49	10,468 (6.7)	1,744 (5.1)
50–59	23,271 (14.9)	4,150 (12.1)
60–69	41,866 (26.9)	7,938 (23.1)
70–79	52,530 (33.7)	11,795 (34.4)
80+	23,402 (15.0)	7,121 (20.7)
Gender (n, %)		
Female	84,924 (54.5)	15,171 (44.2)
Male	70,989 (45.5)	19,160 (55.8)

(*Continued*)

Table 1 (Continued).

Demographics	Solid Tumor (N = 155,913)	Hematological Malignancy (N = 34,331)
Race and ethnicity (n, %)		
Non-Hispanic White	111,064 (71.2)	24,717 (72.0)
Non-Hispanic Black	19,935 (12.8)	4,134 (12.0)
Non-Hispanic Asian	3,950 (2.5)	801 (2.3)
Hispanic	12,918 (8.3)	3,018 (8.8)
Missing/unknown	8,046 (5.2)	1,661 (4.8)
Insurance type (n, %)		
Commercial	55,458 (35.6)	11,345 (33.1)
MAPD	100,455 (64.4)	22,986 (67.0)
Region (n, %)		
Northeast	22,255 (14.3)	4,894 (14.3)
Midwest	42,880 (27.5)	9,996 (29.1)
South	72,805 (46.7)	15,250 (44.4)
West	17,905 (11.5)	4,178 (12.2)
Other	68 (<0.1)	13 (<0.1)
Mean baseline Charlson comorbidity score (SD)	5.7 (2.7)	4.1 (2.4)
Median baseline Charlson comorbidity score (Q1– Q3)	6.0 (3.0–8.0)	3.0 (2.0–6.0)
Baseline Charlson comorbidity score (categorical)		
0	1,514 (1.0)	393 (1.1)
1–2	26,340 (16.9)	11,522 (33.6)
3–4	25,431 (16.3)	10,550 (30.7)
5+	102,628 (65.8)	11,866 (34.6)
Index medication class (n, %)		
Interleukin inhibitors	553 (0.4)	62 (0.2)
Janus kinase inhibitors	38 (<0.1)	4 (<0.1)
TNF inhibitors	738 (0.5)	62 (0.2)
Other selective immunosuppressants	2,380 (1.5)	3,573 (10.4)
Azathioprine	499 (0.3)	55 (0.2)
Calcineurin inhibitors	503 (0.3)	339 (1.0)
Mycophenolic acid	426 (0.3)	75 (0.2)
Anthracyclines	1,408 (0.9)	76 (0.2)
Checkpoint inhibitors	11,645 (7.5)	343 (1.0)

(*Continued*)

Table 1 (Continued).

Demographics	Solid Tumor (N = 155,913)	Hematological Malignancy (N = 34,331)
Cyclophosphamide	278 (0.2)	207 (0.6)
Protein kinase inhibitors	10,229 (6.6)	4,689 (13.7)
Other cancer therapies	80,683 (51.8)	8,593 (25.0)
Rituximab	972 (0.6)	4,067 (11.9)
Targeted cancer therapies	9,283 (6.0)	1,546 (4.5)
Oral glucocorticoids	5,534 (3.6)	1,700 (5.0)
Multiple	30,744 (19.7)	8,940 (26.0)
Cancer type, n(%)		
Other solid cancer	43,911 (28.2)	-
Breast cancer	33,292 (21.4)	-
Lung cancer	28,250 (18.1)	-
Colorectal cancer	20,305 (13.0)	-
Prostate cancer	12,806 (8.2)	-
Non-melanoma skin cancer	9,753 (6.3)	-
Bladder cancer	8,892 (5.7)	-
Pancreatic cancer	7,473 (4.8)	-
Kidney cancer	5,236 (3.4)	-
Endometrial cancer	4,824 (3.1)	-
Skin melanoma	4,525 (2.9)	-
Liver cancer	4,329 (2.8)	-
Thyroid cancer	1,497 (1.0)	-
Non-Hodgkin lymphoma	-	14,610 (42.6)
Multiple myeloma	-	7,019 (20.5)
Chronic lymphocytic leukemia	-	4,788 (14.0)
Other leukemia	-	3,976 (12.0)
Myelodysplastic syndrome	-	3,150 (9.2)
Acute myeloid leukemia	-	2,235 (6.5)
Chronic myeloid leukemia	-	2,037 (5.9)
Hodgkin lymphoma	-	1,611 (4.7)
Acute lymphocytic leukemia	-	699 (2.0)

Note: Cancer type was identified by ≥2 non-diagnostic claims for the same ICD-10 diagnostic code for primary cancer on different days during the baseline.

Abbreviations: ICD-10, International Classification of Disease, 10th Revision, Clinical Modification; MAPD, Medicare Advantage Part D; N, total number of patients with the specified cancer type; n, number of patients with the specified characteristic; Q, quartile; SD, standard deviation; TNF, tumor necrosis factor.

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HZ Incidence

Patients with a solid tumor or a hematological malignancy had a median follow-up time of 372 days (IQR: 156–786) and 460 days (IQR: 188–959), respectively. The median time to HZ diagnosis was similar in both cohorts, with 328 days (IQR: 135–642) in patients with solid tumors and 320 days (IQR: 121–700) in patients with hematological malignancies, and the condition was most frequently diagnosed in an ambulatory setting: 77.3% and 74.6% for those with solid tumors and hematological malignancies, respectively.

The overall incidence of HZ cases in patients with hematological malignancies was 31.1 per 1,000 PY (95% CI: 29.64–32.52) and 20.9 per 1,000 PY (95% CI: 20.33–21.52) in patients with a solid tumor (Table 2). Among the latter,

Table 2 Incidence of New Herpes Zoster Cases by Cancer Type

Condition	Events	Person-Time	Rate per 1,000 (95% CI)
Solid tumor (N = 155,913)			
Overall	4,793	229,077	20.92 (20.33–21.52)
Lung cancer	904	32,037	28.22 (26.41–30.12)
Non-melanoma skin cancer	398	16,745	23.77 (21.49–26.22)
Endometrial cancer	174	7,585	22.94 (19.66–26.61)
Thyroid cancer	56	2,483	22.55 (17.03–29.28)
Other solid cancer	1,274	56,883	22.40 (21.18–23.66)
Breast cancer	1,271	59,847	21.24 (20.09–22.44)
Prostate cancer	361	18,788	19.21 (17.28–21.30)
Skin melanoma	130	6,900	18.84 (15.74–22.37)
Pancreatic cancer	121	6,675	18.13 (15.04–21.66)
Kidney cancer	130	7,366	17.65 (14.74–20.96)
Colorectal cancer	538	32,073	16.77 (15.39–18.25)
Liver cancer	65	4,434	14.66 (11.31–18.69)
Bladder cancer	202	13,927	14.50 (12.57–16.65)
Hematological malignancy (N = 34,331)			
Overall	1,819	58,574	31.06 (29.64–32.52)
Non-Hodgkin lymphoma	879	24,864	35.35 (33.05–37.77)
Chronic lymphocytic leukemia	304	8,669	35.07 (31.24–39.24)
Multiple myeloma	407	12,300	33.09 (29.95–36.47)
Acute lymphocytic leukemia	34	1,034	32.87 (22.76–45.93)
Acute myeloid leukemia	78	2,482	31.43 (24.84–39.22)
Other leukemia	184	6,672	27.58 (23.74–31.86)
Hodgkin lymphoma	62	2,777	22.33 (17.12–28.62)
Myelodysplastic syndrome	86	4,208	20.44 (16.35–25.24)
Chronic myeloid leukemia	74	4,489	16.48 (12.94–20.69)

Note: rates per 1,000 person-years at risk.
Abbreviations: CI, confidence interval; N, total number of patients with the specified cancer type.

Table 3 Incidence of New Herpes Zoster Cases by Medication Class

	Solid Tumor (N = 155,913)			Hematological Malignancy (N = 34,331)		
	Events	Person-Time	Rate per 1,000 (95% CI)	Events	Person-time	Rate per 1,000 (95% CI)
Mycophenolic acid	34	844	40.30 (27.91–56.31)	8	152	52.75 (22.77–103.93)
Azathioprine	37	1,155	32.05 (22.56–44.17)	9	108	83.31 (38.09–158.14)
Oral glucocorticoids	225	7,120	31.60 (27.61–36.01)	93	2,693	34.54 (27.88–42.31)
Cyclophosphamide	12	433	27.74 (14.33–48.45)	9	297	30.25 (13.83–57.43)
Other selective immunosuppressants	115	4,473	25.71 (21.23–30.86)	191	6,684	28.58 (24.67–32.93)
Rituximab	45	1,848	24.35 (17.76–32.59)	263	7,757	33.90 (29.93–38.26)
Calcineurin inhibitors	28	1,177	23.78 (15.80–34.37)	16	635	25.21 (14.41–40.94)
Multiple	1,059	46,792	22.63 (21.29–24.04)	548	14,741	37.18 (34.13–40.42)
TNF inhibitors	38	1,732	21.94 (15.53–30.12)	2	126	15.90 (1.93–57.44)
Other cancer therapies	2,310	112,917	20.46 (19.63–21.31)	369	12,466	29.60 (26.66–32.78)
Checkpoint inhibitors	253	13,281	19.05 (16.77–21.55)	12	390	30.74 (15.89–53.70)
Protein kinase inhibitors	305	16,101	18.94 (16.88–21.19)	227	9,658	23.50 (20.55–26.77)
Targeted cancer therapies	293	18,369	15.95 (14.18–17.89)	68	2,670	25.47 (19.78–32.28)
Anthracyclines	28	1,950	14.36 (9.54–20.76)	2	91	21.95 (2.66–79.29)
Interleukin inhibitors	11	809	13.60 (6.79–24.34)	2	101	19.88 (2.41–71.80)
Janus kinase inhibitors	0	77	0.00 (0.00–38.76)	0	6	0.00 (0.00–530.28)

Note: rates per 1,000 person-years at risk.
Abbreviations: CI, confidence interval; N, total number of patients with the specified cancer type; TNF, tumor necrosis factor.

HZ rates were highest in patients with lung cancer (28.2 [95% CI: 26.41–30.12] per 1,000 PY), non-melanoma skin cancer (23.8 [95% CI: 21.49–26.22] per 1,000 PY) and endometrial cancer (22.9 [95% CI: 19.66–26.61] per 1,000 PY). For patients with hematological malignancies, HZ rates were highest in patients with non-Hodgkin lymphoma (35.4 [95% CI: 33.05–37.77] per 1,000 PY), chronic lymphocytic leukemia (35.1 [95% CI: 31.24–39.24] per 1,000 PY), multiple myeloma (33.1 [95% CI: 29.95–36.47] per 1,000 PY), acute lymphocytic leukemia (32.9 [95% CI: 22.76–45.93] per 1,000 PY), or acute myeloid leukemia (31.4 [95% CI: 24.84–39.22] per 1,000 PY). Across both cohorts, medication classes associated with the highest HZ incidence rates were mycophenolic acid, azathioprine, and oral glucocorticoids; however, patients on multiple medications had notably high incidence rates among those with hematological malignancies (Table 3).

HZ incidence also tended to increase with age and with the number of immunosuppressive medications used (Table S2). In terms of HZ-related complications, PHN was the most frequently observed condition (20.1% [solid tumor] and 25.9% [hematological malignancies]), followed by HZO (9.3% and 8.1%) (Figure S3).

HZ Hazard Ratios

Patients were more likely to develop HZ during periods when they were using immunosuppressive medications compared to when immunosuppressive medications were not used, both in the solid tumor group (adjusted hazards ratio [HR] 3.2, 95% CI: 3.01–3.39, $p < 0.001$) and the hematological malignancy cohort (adjusted HR 3.2, 95% CI: 2.89–3.57, $p < 0.001$) (Figures 1 and 2). Similar results were observed in unadjusted models as well (data not shown). Among those with a solid tumor cancer, patients with liver or kidney cancer were less likely to have HZ following

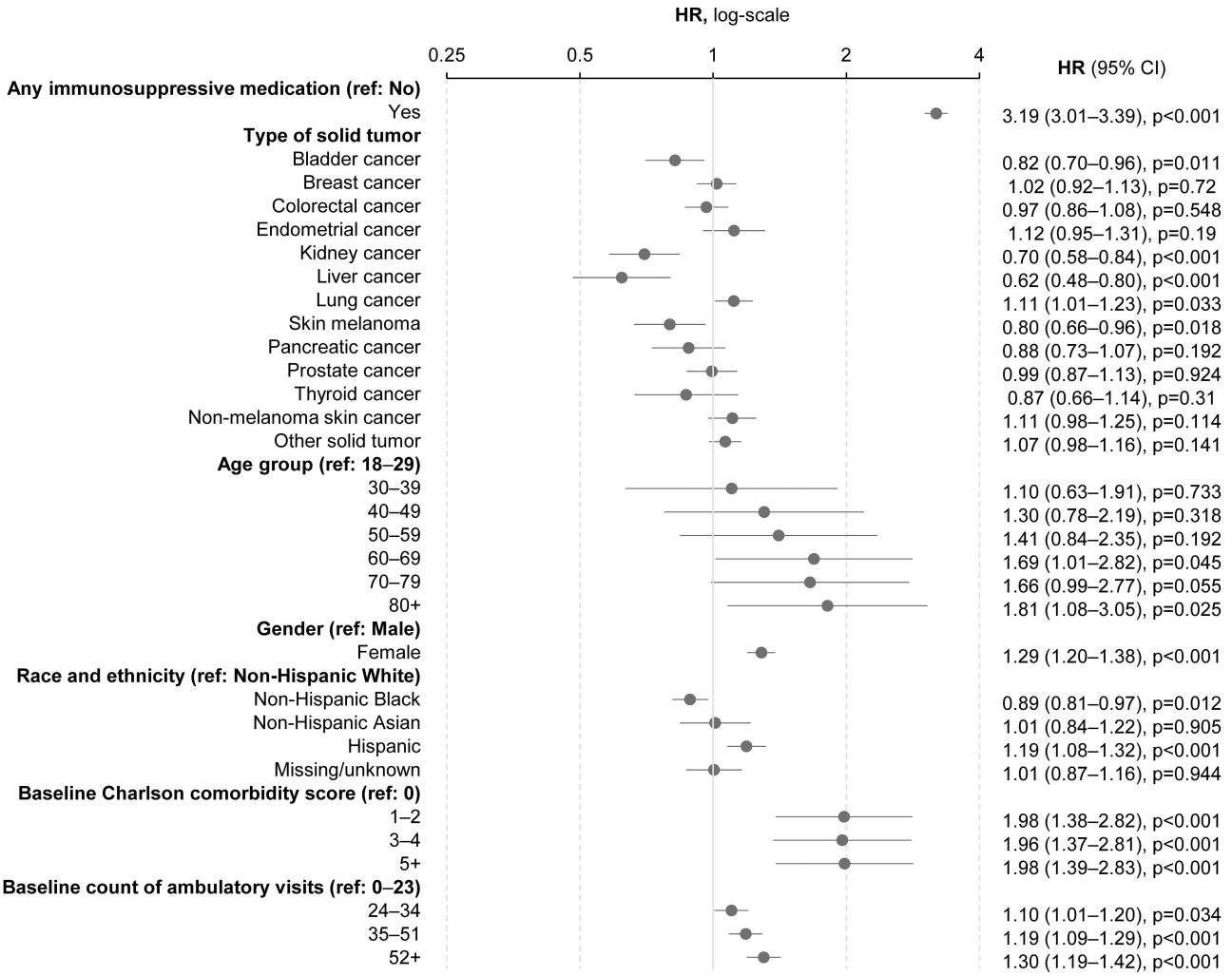

Figure 1 Adjusted herpes zoster hazard ratios in patients with solid tumor cancer.
Note: For each solid tumor type, the reference was those with another solid tumor type.
Abbreviations: CI, confidence interval; HR, hazard ratio; ref, reference.

immunosuppressive therapy initiation compared to patients with other cancer types (Figure 1). Among patients with a hematological malignancy, those with either chronic myeloid leukemia or chronic myelodysplastic syndrome were less likely to experience HZ compared with patients with other hematological malignancies (Figure 2). Additionally, the likelihood of developing HZ increased with age, the number of baseline outpatient visits, and, in patients with solid tumors, was higher among those with a CCI of ≥1 (Figures 1 and 2).

Discussion

This retrospective study focused on HZ incidence in patients with cancer following initiation of immunosuppressive therapy. Compared to the rate of HZ observed in the general immunocompetent population aged ≥50 years (8.5 cases per 1,000 PY),[4] HZ incidence rates across all cancer types in this study were noticeably higher. These results are in line with previous studies, which also reported elevated HZ incidence rates in populations with solid tumor or hematological cancers. For instance, a retrospective cohort study examining cancer patients of Kaiser Permanente Northern California reported an incidence of 12 and 31 HZ cases per 1,000 PY in patients with solid tumors or hematological malignancies, respectively, with standardized HZ rates 1.9 and 4.8 times higher than in the general US population.[8] In a population-based study, HZ incidence rates were 11.0 per 1,000 PY (95% CI: 10.73–11.22) in patients with solid organ neoplasia and 12.0 per 1,000 PY (95% CI: 11.48–12.52) in those with hematological neoplasia.[27] Additionally, in another retrospective

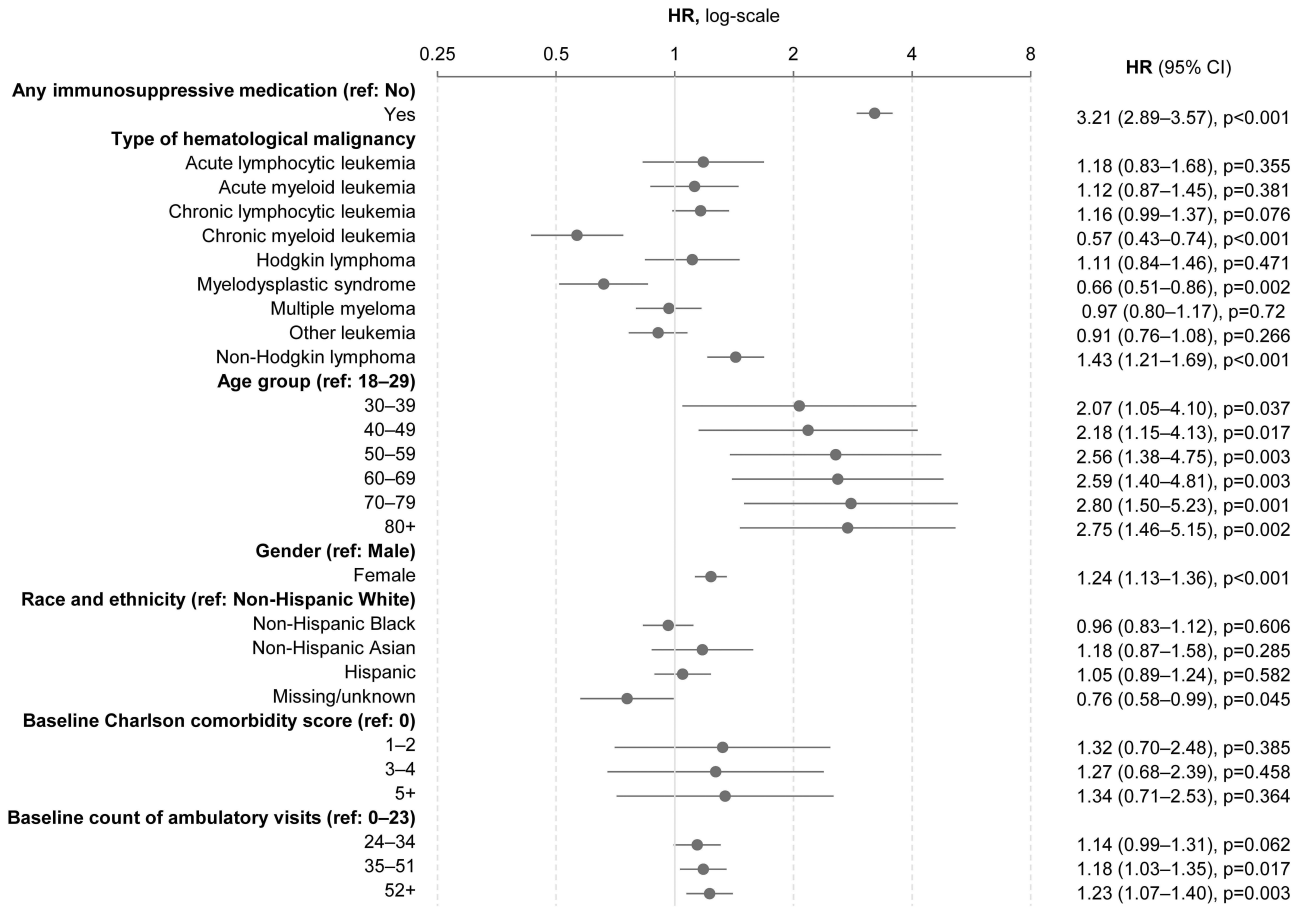

Figure 2 Adjusted herpes zoster hazard ratios in patients with hematological malignancies.
Note: For each type of malignancy, the reference was those with another malignancy type.
Abbreviations: CI, confidence interval; HR, hazard ratio; ref, reference.

claims study, patients with solid tumors receiving chemotherapy had an adjusted HZ incidence rate of 13.8 per 1,000 PY.[11] This also aligns with the results of a meta-analysis showing that cancer patients had increased odds (OR: 2.4, 95% CI: 1.91–3.07) of HZ compared to individuals without these conditions.[10]

In the current study, mycophenolic acid, azathioprine, oral glucocorticoids, TNF inhibitors, and rituximab were associated with elevated HZ rates, much of which reflects findings from similar studies involving these treatments.[12–14,28,29] This illustrates the extended health burden in terms of HZ risk in patients resorting to immunosuppressive medication, which compounds the HZ risk due to their underlying condition. For immunosuppressed patients with HZ, antiviral therapy is recommended,[30] however, prevention of this debilitating disease would be better.

Preventive strategies against HZ are recommended by several national organizations, most notably the Advisory Committee on Immunization Practices, which, since October 2021, recommends 2 doses of recombinant zoster vaccine (RZV) for the prevention of HZ and related complications in individuals aged ≥19 years who are or will be immunodeficient or immunosuppressed due to disease or therapy.[31] In adult cancer patients who received 2 doses of RZV during or after immunosuppressive treatment, RZV showed 87.2% efficacy against HZ.[32] In 2024, the American Society of Clinical Oncology stated that RZV should be made available to all adults with solid tumors or hematological malignancies, including patients previously vaccinated with the live zoster vaccine before their cancer diagnosis. Ideally, RZV is administered immediately after the diagnosis and before the start of immunosuppressive therapy, while the interval between the doses can be reduced to 4 weeks if required for the planned cancer treatment regimen.[33]

Given the observed HZ incidence rates, the results of the current study reinforce the importance of HZ prevention strategies outlined by these national entities, specifically the need for all providers managing the care of patients with

cancer to coordinate vaccination-related efforts. Based on the current findings, future studies should design and test provider workflow strategies that identify patients eligible for HZ vaccination, determine the appropriate timing of the vaccinations in accordance with the latest guidelines, and then assist patients in accessing the vaccine to improve the odds of uptake.

The findings of this study should be interpreted bearing several limitations in mind. First, as a study using administrative claims data, immunosuppressive treatments were identified through pharmacy and medical claims, which may not accurately reflect primary exposure, as medication use, timing, and adherence cannot be confirmed. Additionally, other medications not captured in this study may also affect immunocompetency, while some included therapies, such as protein kinase inhibitors and checkpoint inhibitors, may not be inherently immunosuppressive but do have immune-modulating effects. Second, patient data selected for the study were among those not vaccinated and enrolled in a commercial or MAPD health plan during the study period. Therefore, the results may not be applicable to uninsured populations or a real-world population including vaccinated individuals. Third, using diagnosis codes to detect incident cases of HZ has limited sensitivity, which may result in underestimating HZ incidence. Fourth, it was not documented whether the cancer diagnoses and treatments considered in this study were each patient's first cancer diagnosis and immunosuppressive treatment. Previous cancer treatment may affect HZ risk, which may result in under- or overestimating HZ incidence. In a future study, stratifying for the number of cancer diagnoses and treatments should be considered to determine the effect on HZ incidence. Finally, medical histories may be incomplete for certain patients, resulting in their misclassification as non-vaccinated, and certain socioeconomic data elements may be missing for some individuals in the claims database, leading to potential inaccuracies in the assignment of socioeconomic status and pre-defined categorizations. While measures were taken to limit selection bias, some of the methods used may have inadvertently led to some biased results (eg, analysis of HZ complications was restricted to patients with at least certain months of follow-up).

This is the first study that analyzed HZ risk in cancer patients after the start of immunosuppressive therapy. Previous studies analyzed HZ risk in cancer patients, where some patients were on immunosuppressive therapy, and noted that immunosuppression increased HZ risk.[8,34] However, those studies lacked the comprehensive stratification by type of cancer and treatment regimen provided in this study, which, consequently, provides specific evidence that strengthens the literature and will aid in patient management.

Conclusions

This study observed elevated risk of HZ in cancer patients initiating immunosuppressive therapy, and a higher HZ incidence associated with several immunosuppressive medications used among those with solid tumors or hematological malignancies. These findings provide oncologists and hematologists with a broader perspective on potentially immunosuppressive medications their patients may be taking, aiding in a more comprehensive assessment of patient management and care. Given such elevated risk, HZ prevention through vaccination needs to be prioritized in US adults with solid tumors and hematological malignancies, irrespective of their age.

Abbreviations

AHRQ, Agency for Healthcare Research and Quality; CCI, Quan-Charlson comorbidity score; CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; ICD-10, International Classification of Diseases, Tenth Revision, Clinical Modification; IQR, interquartile range; MAPD, Medicare Advantage with Part D; OR, odds ratio; PHN, postherpetic neuralgia; PY, person-years; RZV, recombinant zoster vaccine; SD, standard deviation; TNF, tumor necrosis factor; US, United States.

Data Sharing Statement

Data used for this publication was generated by Optum. The data contained in Optum Research Database contains proprietary elements owned by Optum and, therefore, cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third party clients assumes certain data security and privacy protocols are in place and that

the third party client has executed Optum's standard license agreement which includes restrictive covenants governing the use of the data.

Ethics Approval and Informed Consent

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 in tabular form and presented as aggregate analyses that omit subject identification, therefore informed consent, ethics committee or Institutional Review Board approval was 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; had full access to the data and 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. 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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