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Herpes zoster risk in immunocompromised adults in the United States: A systematic review

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Abstract

Background: The primary reported risk factors for herpes zoster (HZ) are increasing age and immunodeficiency yet estimates of HZ risk by immunocompromising condition have not been well characterized. We undertook a systematic review of the literature to estimate HZ risk in five categories of immunocompromised patients.

Methods: We systematically reviewed studies examining risk of HZ and its complications in adult patients with hematopoietic cell transplants (HCT), cancer (hematologic and solid tumor), HIV, and solid organ transplant (SOT; kidney and other). We identified studies in Pubmed, Embase, Cochrane, Scopus, and clinicaltrials.gov that presented original data from studies in the United States published after 1992 (1996 for HIV). We assessed risk of bias with Cochrane or GRADE methods.

Results: We identified and screened 3,765 records and synthesized 34 studies with low or moderate risk of bias. The majority of studies included (32/34) reported at least one estimate of HZ cumulative incidence (range=0%–41%). Twelve studies reported HZ incidence, which varied widely within and between immunocompromised populations. Incidence estimates ranged between 9 and 92 HZ cases/1,000 patient-years and were highest in HCT, followed by hematologic malignancies, SOT, solid tumor malignancies, and lowest in HIV patients. Among 17

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studies of HCT patients, absent or <1 year of post-transplant antiviral prophylaxis were associated with higher HZ cumulative incidence.

Conclusions: HZ is common among all immunocompromised populations studied— exceeding expected HZ incidence among immunocompetent adults ≥60 years. Better evidence of incidence of HZ complications and severity in immunocompromised populations are needed to inform economic and HZ vaccine policy analyses.

Summary:

Herpes zoster (HZ) incidence among immunocompromised populations has not been precisely estimated. We performed a systematic review to assess HZ incidence and complications among five categories of immunocompromised patients. Our findings have practice and prevention implications.

Keywords

Herpes zoster; immunocompromised; Postherpetic neuralgia; VZV; RZV

Introduction

Herpes zoster (HZ) is a painful rash illness, which results from reactivation of latent varicella zoster virus (VZV). In the United States (US), about 1 million cases of HZ occur each year and nearly 1 in 3 people will experience HZ in their lifetime[1]. The primary risk factors for HZ are advanced age and immunosuppression. Increasing HZ incidence with age has been well defined, however, the risk for HZ conferred by immunocompromising conditions or immunosuppressive drugs has not been as well defined[2–4].

Immunosuppression is also known to increase the incidence of HZ complications and disease severity. The most common HZ complication is postherpetic neuralgia (PHN), a painful, persistent condition that can substantially affect quality-of-life among the aged, and has been shown to be more common among immunosuppressed patients[5, 6]. HZ may also require hospitalization when it presents with severe ocular/otic complications, and among immunosuppressed patients when it is more likely to present with life-threatening complications such as encephalitis and disseminated disease (rash in ≥3 dermatomes)[7, 8].

Two vaccines are licensed and recommended in the US to prevent HZ and its complications; one is live-attenuated (ZVL) and the other recombinant (RZV). Although live-attenuated vaccines like ZVL are contraindicated in immunocompromised patients, use of RZV in these populations is being tested in clinical trials. The Advisory Committee on Immunization Practices (ACIP) and other medical associations have not yet made recommendations regarding RZV use in immunocompromised populations[9, 10].

An estimated 3 million Americans live with primary, acquired, or iatrogenic immunocompromising conditions[11, 12]. An additional 22 million people with autoimmune or inflammatory conditions may receive immunosuppressive therapies[13, 14]. Therefore, the population at higher risk for HZ is substantial but estimating burden of disease requires a clear understanding of HZ incidence and severity. To synthesize available

data, we conducted a systematic review of published studies to assess the risk of HZ and its complications among adults with selected immunocompromising conditions in the US.

Methods

Literature search

We performed a literature search in PubMed, EMBASE, OVID Medline, Scopus, Clinicaltrials.gov, and Cochrane Library using HZ terms and immunocompromising conditions among studies published between January 1, 1993, and January 8, 2019 outlined in a supplemental table. References cited by the retrieved articles for were searched for additional references.

Inclusion and exclusion criteria

We included full-text, original research articles reporting data on HZ risk in at least one of five immunocompromised U.S. adult populations (hematopoietic stem cell transplant recipients [HCT], hematologic malignancies [HM], solid organ transplant [SOT], solid tumor malignancies [STM], or people living with HIV). Clinical trials of HZ vaccination were included even if they had study sites outside the US, and estimates of HZ risk among unvaccinated (placebo) groups. We excluded studies limited to children or the elderly (>65 years). We excluded abstracts, case reports, and animal or molecular studies. For studies in HIV patients, we excluded estimates from populations not receiving standard antiretroviral therapy (ART).

Data extraction and Outcomes

Reviewers assessed studies for eligibility and then abstracted information on setting, design, demographics, antiviral prophylaxis, and outcomes using a standardized abstraction worksheet.

We extracted outcome measures for HZ risk, and post-herpetic neuralgia (PHN), disseminated HZ, HZ ophthalmicus, and hospitalization. HZ risk was measured as either cumulative incidence (the number of cases reported during the specified follow-up period, as a percentage of all study participants) or incidence (cases per 1,000 person-years). We defined PHN as pain lasting >90 days after HZ and reported PHN as a proportion of total HZ cases. We relied on the authors' definitions for disseminated disease, HZ ophthalmicus and when hospitalizations were due to HZ.

Quality assessment

We evaluated study design, outcome definition, adequate adjustment of confounding factors, generalizability of the findings and risk of bias. Observational studies and open-label phase 1 and 2 clinical trials were evaluated for methodological issues specified by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [15]. The risk of bias for clinical trials was assessed according to guidelines of the Cochrane Collaboration [16]. We rated a study low-risk of bias if it had 0 categories or 1 category with minor issues, moderate if 1 or 2 categories were selected, or high if 3 or more categories were selected or if 1 category had critical problems. Data abstraction and risk of bias

assessments were performed by SM, AG, or KD; extracted data were assessed for accuracy by a second reviewer. All reviewers adjudicated any data discrepancies identified during the second review.

Results

Study Characteristics

Of the 3,765 studies screened, 869 full-text articles and identified 57 studies were eligible for inclusion and data extraction (figure 1). Characteristics of these studies are summarized in the table 1[17–72]. Among the 57 articles abstracted, 19 were clinical trials and 38 observational. The median study size was 49 (interquartile range [IQR]=27–78) for clinical trials (excluding populations who received vaccine as an intervention) and 355 (IQR=122–1739) for observational studies. Five studies (9%) reported a median or average study population age ≥65 years old, while 25 studies (45%) reported a median or average study population age of ≤50 years.

We assessed each study for risk of bias and classified 23 studies as high, 19 moderate, and 15 low-risk. Subsequent description of outcomes and figures report estimates from the 34 studies we deemed to have low or moderate-risk of bias since these were more likely to report valid and generalizable estimates.

HZ cumulative incidence

Most studies included (32/34) reported the total number of zoster cases that occurred during the study period (cumulative incidence). A total of 40 cumulative incidence estimates were reported: 16 for HCT; 11 for SOT; 5 for HM; 4 for STM; and 4 for HIV (figure 2)[18, 20, 22, 24–26, 29, 30, 32, 35–38, 40, 41, 49, 51, 52, 55, 58–60, 62, 64, 65, 67–73]. The cumulative incidence of HZ ranged from 0% to 41% (IQR=2–13%). Follow-up time reported as median, average, or maximum was categorized into <1 year, 1 to 2 years, or >2 years. The point estimates generally increased with increasing follow-up time: <1 year (median=3.6%, IQR=1–4%, n=7), 1 to 2 years (median=6%, IQR=2–13%, n=21), and >2 years (median=13.7%, IQR=8–19%, n=9). Among study populations with no reported HZ cases, 3/6 were from clinical trials with active follow-up [21, 55]. Interim cumulative incidence estimates when reported, showed that the risk of HZ is not constant over time, with the highest risk occurring in the first 2 years of follow-up[25, 41, 70].

The 6 highest estimates of cumulative incidence were reported in HCT recipients ([22, 25, 38, 41, 62, 71]. Among HCT recipients, the risk varied by transplant type; 12 articles reported cumulative incidence estimates for autologous HCT (median 18.6%; IQR=11–23%) and 5 estimates for allogeneic HCT (median 9%; IQR=4–25%)[22, 25, 30, 32, 38, 40, 41, 55, 58, 60, 62, 64, 65, 68, 71, 73]. All estimates for HM, STM, and HIV were below 10%, but estimates varied within the immunocompromising category. Among SOT recipients, the HZ risk ranged from 0 to 16% and varied depending on the organ transplanted (e.g. heart, kidney, liver, and other visceral transplants)[18, 37, 42, 49, 59, 67, 70]. The highest risk was reported for heart transplant recipients (16% and 11%). Most reported estimates were for kidney transplants (n=3, median 5%)[19, 38, 68].

HZ Incidence rates

Thirteen studies reported 15 incidence rates of HZ: 4 estimates for HCT; 2 for HM; 4 for SOT; 3 for STM; and 2 for HIV (figure 3)[18, 24, 29, 35, 36, 41, 42, 51, 59, 62, 69, 71–73]. The incidence rate of HZ ranged between 9 and 95/1,000 person-years (PY). Incidence rates exceeding 40/1,000 PY were reported for both HCT and HM populations with the highest estimates from placebo recipients in phase III clinical trial studies who underwent active follow-up [35, 71]. Other populations of immunocompromised patients had median HZ incidence estimates <30/1,000 PY. Two studies reported HZ incidence for more than one immunocompromising population. Chen et al. reported estimates for multiple immunocompromised populations and found that the incidence of HZ in HCT populations (43/1,000 PY) was nearly 3 times that of SOT or HIV populations (each 17/1,000 PY)[29]. Habel et al. reported an incidence of HZ in HM patients (31/1,000 PY) over two times higher than that for STM patients (12.3/1,000 PY)[36].

Only one study in our review, reported data that allowed for comparison of the risk for HZ by age group across immunocompromising groups. Here, the incidence (per 1,000 PY) for those aged 18–49 years versus 60–64 years was: HCT (40 vs 51), SOT (13 vs 20) HIV (18 vs 16) cancer (8 vs 13)[29].

Post-herpetic neuralgia (PHN)

Twelve studies reported 14 estimates of the proportion of HZ cases that developed PHN according to our definition of pain lasting >90 days after HZ[26, 29, 36, 40–42, 52, 59, 62, 68, 71, 73]. The risk of developing PHN ranged between 6% and 45% across the immunocompromising conditions. Within each of the immunocompromising categories there was heterogeneity between PHN estimates; HCT (range = 6–41%, n=6), SOT (range = 7–45%, n=3), HM (range = 6–40%, n=3), STM (9%, n=1) and HIV (6%, n=1). Although PHN estimates varied between studies, estimates within a single study were similar to one another; Chen et al. reported PHN estimates for HCT (10%), SOT (7%), and HIV (6%)[29], and Habel et al. reported PHN for STM (9%) and HM (6%) populations[36].

Disseminated HZ

Eighteen studies reported 25 estimates for occurrence of disseminated HZ[18, 22, 24–26, 30, 32, 36, 40–42, 52, 60, 62, 64, 68, 71, 73]. The majority of estimates (n=18) were among HCT recipients and ranged from 0% to 32%, with a median of 3% (IQR=0.2–3.8%)[22, 25, 30, 32, 40, 41, 60, 62, 64, 68, 71, 73]. Two recent large randomized clinical vaccine trials in autologous HCT patients reported 2% and 4% disseminated HZ, respectively[71, 73]. Truong et al. retrospectively analyzed rates of HZ following autologous HCT and found that patients on the least stringent prophylaxis regimen (until neutrophil recovery ≥500/μL) had the highest rate of disseminated disease (4%) compared with none with prophylaxis of 6 months or longer[68, 73].

HZ ophthalmicus and hospitalization

Four studies reported 7 estimates for ocular HZ complications which were ≤1%[32, 42, 62, 71]. Erard et al. retrospectively reviewed medical records of three HCT cohorts receiving prophylaxis regimens of increasing duration and reported no ocular complications (n=2,635)

[32]. HZ-associated hospitalization was reported by two studies. Arness et al. reported that among 37 cases of HZ in kidney transplant patients, 7 (19%) individuals were hospitalized[18]. In a vaccine clinical trial, Winston et al. reported that among 113 individuals who developed HZ after HCT, 16 (14%) were hospitalized[71].

Antiviral prophylaxis and HZ risk

Seventeen studies conducted on HCT patients provided 34 estimates of cumulative incidence of HZ post-transplant[22, 25, 30, 32, 38, 40, 41, 55, 58, 60, 62, 64, 65, 68, 71–73]. The HZ risk estimates are plotted by follow-up time, prophylaxis duration, and population size (figure 4). Overall, the cumulative incidence of HZ increased with increased follow-up time. The duration of antiviral prophylaxis appears to modify risk of HZ; HCT patients who received short-term prophylaxis had the highest cumulative incidence of zoster at a given follow-up time. The effect of long-term prophylaxis against HZ persists at one year after prophylaxis is discontinued[25, 32, 40], however Boeckh et al. found that by 5 years post-transplant, the HZ risk of patients who received 12 months of prophylaxis was similar to that of patients who received no prophylaxis.

Discussion

Our systematic review of HZ risk among adults with 5 major immunocompromising conditions found 57 eligible studies, 34 of which we deemed to have low or medium-risk of bias. HZ incidence estimates were highest among HCT patients, followed by HM and then SOT, STM and HIV patients. Median incidence estimates for all groups reviewed here exceed those reported for immunocompetent adults >50 years old [1]. In fact, estimates for the incidence of HZ following HCT were 6–10 times that for the U.S. adult population. The volume of medical literature described here indicates that the field recognizes the significance of HZ among immunocompromised populations. However, this work is the first to attempt to systematically assess the overall risk of HZ in immunocompromised patients in the US.

There was large variation in study estimates for cumulative incidence and incidence of HZ within each immunocompromised category. This variation is likely due to numerous factors including study design, case ascertainment, antiviral prophylaxis regimen, follow-up duration and quality, and characteristics of the patient populations including underlying condition, transplant type, complications, comorbidities, and age. In addition, over the last 25 years there have been significant improvements in treatment options for immunocompromising conditions that make comparisons across studies challenging. Administrative or electronic medical record databases allow efficient study of large populations but lack clinical and other data necessary to assess accuracy, and despite adjustments, often have residual confounding. Case-ascertainment and control of bias may be better in randomized clinical studies, however, these study populations are smaller and highly selected, hampering generalizability of results. Given study heterogeneity, we felt that it was inappropriate to pool the estimates in a meta-analysis.

Although recommended antiviral prophylaxis is effective at preventing VZV reactivation after HCT, there is no universal standard prophylactic regimen for HCT recipients and

antiviral drug, duration, and dosage vary[74, 75]. Our analysis of HZ cumulative incidence by prophylaxis regimen underscores that prophylaxis is effective against VZV reactivation post-transplantation. Figure 4 demonstrates this point and illustrates the trend that the populations with highest HZ cumulative incidence received no prophylaxis compared to those receiving some prophylaxis at a given follow-up time. However, studies with follow-up >2 years revealed that the protection wanes after prophylaxis is discontinued, suggesting that preventing HZ with a vaccine may enhance long-term protection. Interpretation of these data are limited by the fact that this is a convenience sample and HZ is affected by other factors not represented in the graph.

Other systematic reviews have also found heterogeneity in HZ risk estimates across immunocompromising conditions[76–78]. Yanni et al. reported zoster risk for 16 immunocompromising conditions in individuals 18–49 years old and found an overall rate of 3.5/1,000 PY–similar to that found for healthy individuals[79]. However, the risk varied among the 16 immunocompromising conditions with the highest risk of 41.7/1,000 PY among HCT patients. Similarly, Forbes et al. found that among adults in the UK, the strongest risk factor for HZ was the underlying immunosuppressive condition, with HCT the highest risk (OR of 13.46; 99% CI=2.68–67.60) compared to matched controls[80]. In addition, an Australian study reported increased risk for zoster in cancer patients; receipt of chemotherapy further increased risk for those with solid organ cancers and increased risk for those with hematological cancers could be detected 2 years prior to cancer diagnosis [81].

Estimates of the risk of HZ complications were less frequently reported in the literature, and few studies reported on recurrent zoster; data were insufficient to assess risk by immunocompromising condition. Disseminated zoster was most frequently studied among complications, however, most estimates come from studies in HCT. PHN, notoriously difficult to study from administrative data, demonstrated wide ranges in estimates. A systematic review by Kawai et al. of HZ in immunocompetent populations reported a similarly wide range of PHN estimates (5% to ≥30%)[82].

Studies reporting ocular complications and hospitalization were infrequent and estimates ranged from 0–1% and 14–19%, respectively. Rare complications, such as HZ encephalitis, may be poorly captured in administrative databases[83]. The opposite is true for hospitalization, which is common for many immunosuppressed populations. However, determining if hospitalization was HZ-related or due to complications of their underlying conditions can be difficult in retrospective reviews that depend on physician notes or administrative claim codes. While our findings make clear that the risk of HZ-associated complications and severe disease are increased in immunocompromised populations, the paucity of high-quality data make it difficult to characterize the true HZ burden in these patients.

Although our analysis suggests that HZ risk can be ordered by immunocompromising condition, risk within each condition varies due to the underlying disease and therapies received. For example, for HCT recipients, HZ risk likely varies depending on the type of transplant received and complications such as graft-versus-host disease, both of which may affect the type and timing of prophylaxis received. Among SOT recipients, risk correlates

with the intensity of immunosuppression, with the highest risk for heart and lung transplants, followed by kidney, and liver[59, 84, 85]. Finally, SOT patients are on lifelong immunosuppressants while those receiving an HCT may be able to discontinue their use, so risk may vary over time among populations. More granular data are needed to address the specific risk factors for unique subpopulations, immunosuppressive regimens, and long-term risk within each immunocompromising condition.

Beyond gaps in reporting on complications and severity of HZ, there were other limitations identified in our review. Many studies (41%) were assessed to be high risk of bias and were not included in our analysis. In those included, we could not control for known risk factors for HZ such as sex and age because demographics for were infrequently reported. Additionally, there are limited data on the risk of HZ for immunocompromised adults <50 years old. We limited our analysis to HCT, SOT, STM, HM, and HIV because these conditions and their treatments are relatively well-defined. However, other immunocompromised patients, such as those with rheumatologic and autoimmune conditions, who are thought to be at increased risk of HZ should be considered for future study.

This review underscores the high risk for HZ among immunocompromised individuals and the gaps in knowledge about HZ complications and severity. Although HZ is thought to be more severe in immunocompromised patients, and early data suggest the benefits of vaccination in some patient populations[73], high quality data on complications and severity are required to evaluate the cost-effectiveness of vaccination for these populations. This additional information will be critical to inform policy decisions for HZ vaccines in immunocompromised populations in the US.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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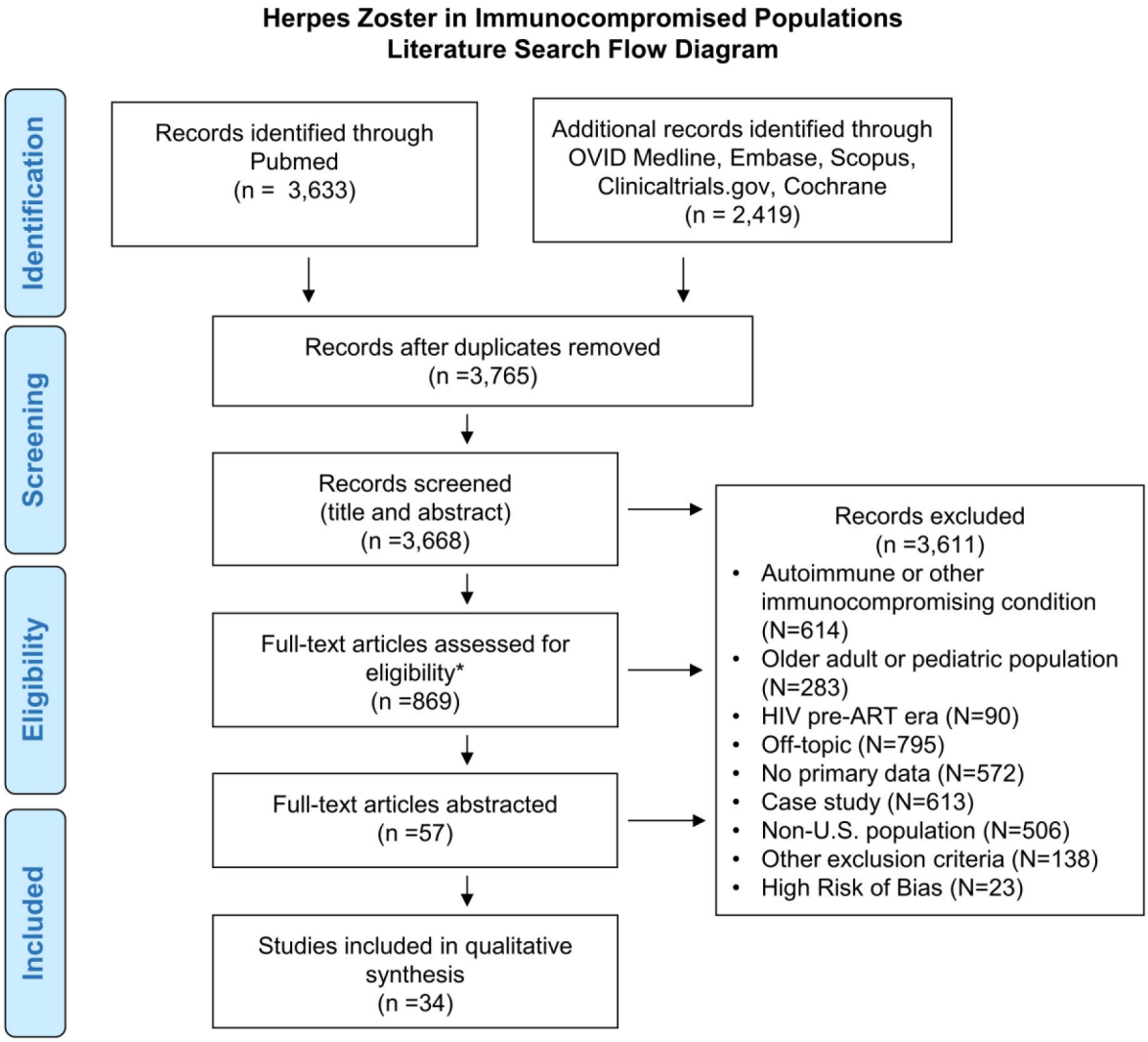

Figure 1: Literature Search Flow Diagram

The flow diagram was adopted from the PRISMA statement[86].

*For the selected immunocompromised groups (HCT, HIV, BC, STM, and SOT)

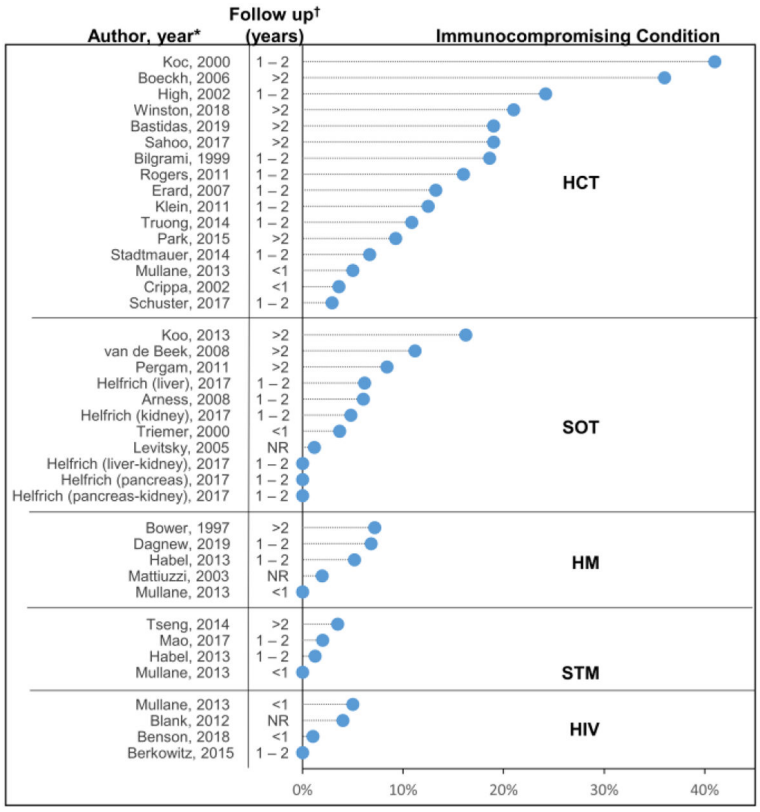

Figure 2: Herpes zoster (cumulative incidence) among patients with selected immunocompromising conditions

Studies reporting herpes zoster cumulative incidence for select immunocompromising conditions.

*Studies with low or medium risk of bias

†follow-up time reported as median, average, or maximum was categorized into <1 year, 1 to 2 years, or >2 years. NR, not reported

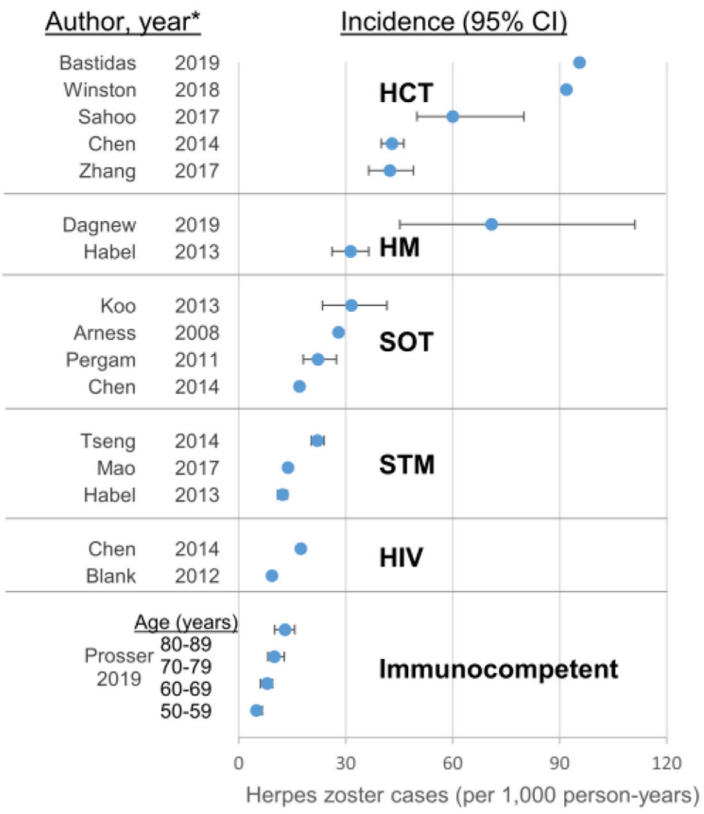

Figure 3: Herpes zoster incidence rates among patients with selected immunocompromising conditions

Herpes zoster incidence rates.

*Studies with low or medium risk of bias

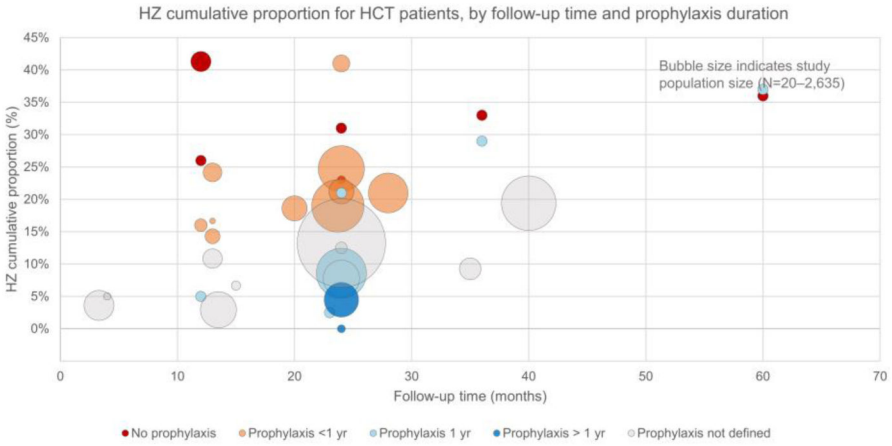

Figure 4: Cumulative incidence of herpes zoster among HCT patients, by time following transplant and duration of prophylaxis

Bubble plot showing cumulative incidence estimates of herpes zoster among HCT patients by post-transplant follow-up time (average, median, or maximum, as reported). Study populations are categorized by prophylaxis duration (average, median, or maximum, as reported). Bubble sizes are proportional to the study population size (range=20–2,635).

Table 1:

Characteristics of Included Studies

Immunocompromised Population	Risk of Bias Rating	Citation Year	Study design (study years)	Study population size Age years (range)*	Length of follow up†
Hematopoietic Stem Cell Transplant (HCT)	Low	Bastidas et al. [73] 2019	Clinical Trial (2012–2017)	924 (placebo) A=55.1 (±11.4)	M=23.7 months
		Chen et al. [29] 2014	Retro Cohort (2005–2009)	51,022,838 A=43	A=1.8 years
		Erard et al. [32] 2007	Retro Cohort (1996–2003)	2,635 Cohort 1: M=42(1–68); cohort 2: M=45(1–74); cohort 3: M=47 (0–73)	90% had 2 or more years
		Klein et al. [40] 2011	Clinical Trial (1998–2001)	53 Placebo: M=46.7 (25.6–68.2) Valacyclovir: M=45 (21.9–66.7)	Up to 2 years post–transplant
		Koc et al. [41] 2000	Retro Cohort (1992–1997)	100 M=38	2 years (0–84+ months)
		Sahoo et al. [62] 2017	Retro Cohort (2002–2010)	1,000 M=55.5	M=39.7 months (3,778.1 PY)
		Schuster et al. [64] 2017	Prosp Cohort (2006–2011)	444 M=53 (18–75)	M=13.5 months
		Stadtmauer et al. [65] 2014	Clinical Trial (2009–2012)	30 (placebo) M=59.5 (30–70)	15 months
		Winston et al. [71] 2018	Clinical Trial (2010–2015)	564 (placebo) A=54; M=56 (19–79)	A=28 months (SD, ±1.3)
	Medium	Bilgrami et al. [22] 1999	Retro Cohort (1993–1997)	215 M=44 (2–65)	M=20 months (1–58 months)
		Boeckh et al. [25] 2006	Clinical Trial NR)	77 Acyclovir: A=29 (10–47) Placebo: A=32 (14–65)	Up to 6 years
		Crippa et al. [30] 2002	Prosp Cohort (1995–1998)	300 CD34 selected: M=51 (6–67) Non-selective: M=47 (2–69)	100 days
		High et al. [38] 2002	Prosp Cohort (NR)	120 A= 46.0 (SD, ±9.7)	Between 14 days and 13 months post–transplant
		Park et al. [58] 2015	Retro Cohort (2008–2013)	162 M=54.5 (23–67)	M=35.3 months
		Rogers et al. [60] 2011	Retro Cohort (2004–2007)	56 M=57 (35–72)	1 year
		Truong et al. [68] 2014	Retro Cohort (2004–2010)	129 PPX cohorts: until neutrophil recovery: M=54 (16–72) 6 months: M=52 (22–72) 1 year: M=55 (26–70)	M=13 months M=13 months M=23 months
		Zhang et al. [72] 2017	Retro Cohort (2009–2014)	1,959 M=58	1 −5 years
	High	Akpek et al. [17] 2001	Retro Cohort (1998–1999*)	50 M=53 (38–71)	≥ 1 year
		Lee et al. [48] 2015	Retro Cohort (2010–2015)	55 M=53 (3–69)	NR
HCT, HIV, HM, STM	Medium	Mullane et al. [55] 2013	Clinical Trial (2007–2010)	79 A=54.1 (19–91)	<120 days

Immunocompromised Population	Risk of Bias Rating	Citation Year	Study design (study years)	Study population size Age years (range)*	Length of follow up†
HIV/AIDS	Low	Benson et al. [20] 2018	Clinical Trial (2009–2011)	99 (placebo) M=49 (IQR=44–55)	<24 weeks
		Berkowitz et al. [21] 2015	Clinical Trial (2010–2013)	49 M=44 (26–71)	18 months
	Medium	Blank et al. [24] 2012	Retro Cohort (2002–2009)	4,353 A=39 (18–68)	19,752 PY
	High	Birlea et al. [23] 2011	Retro Cohort (1995–2003)	180 A=40 (18–71)	none
		Gebo et al. [33] 2005	Retro Cohort (1997–2001)	2,543 M=41	8,777 PY (total for all patients)
		Glesby et al. [34] 2004	Prosp Cohort (1994–2002)	2,321 A=36.8 (16–73)	7.5 years
		Kilbourne et al. [39] 2001	Prosp Cohort (1999–2000)	810 A=49	1 year
		Moanna et al. [54] 2013	Retro Cohort (1997–2009)	2,787 (HAART era) M=45	12 years
		Scarsella et al. [63] 2002	Prosp Cohort (1998–1999)	86 M=41.3 (SD, ±8.6)	NR
Hematologic malignancy (HM)	Low	Bower et al. [26] 1997	Retro Cohort (1987–1991)	962 M/A=62 (29–95)	M=57.5 months (0–420 months)
		Dagnew et al. [35] 2019	Clinical Trial NR	279 (placebo) A=57.8 (SD, ± 14.9)	13 months
	Medium	Mattiuzzi et al. [52] 2003	Retro Cohort (1998–2002)	771 Without VZV: M=52 (15–84) With VZV: M=57 (29–71)	NR
	High	Bartlett et al. [19] 2008	Clinical Trial (2002–2003)	24 M=38 (23–79)	4 weeks
		Byrd et al. [27] 1999	Prosp Cohort (1994–1996)	21 HZ cases: M=67 (51–79)	Up to 40 months
		Kumar et al. [45] 2010	Clinical Trial (2007–2008)	25 M=61 (49–79)	Up to 2 years
		Kurzrock et al. [46] 1999	Clinical Trial NR	28 M=63 (39–78)	Up to 1 year
		Liu et al. [50] 1998	Clinical Trial (1993–1997)	20 M=66 (37–81)	M=28 months (1–37 months)
		McLaughlin et al. [53] 1996	Clinical Trial (1992–1993)	51 M=62	20 months
		Oken et al. [56] 2004	Clinical Trial (1989–1992)	51 M=62 (31–82)	M=9 years (for 11 surviving patients)
HM and STM	Low	Habel et al. [36] 2013	Retro Cohort (2001–2006)	14,670~70% were aged > 60	M=22 months, maximum=6 years
Solid Tumor Malignancy (STM)	Low	Tseng et al. [69] 2014	Retro Cohort (2007–2012)	16,766 M=74.7	30 months
	Medium	Mao et al. [51] 2017	Retro Cohort (2010–2014)	155,480 NR (>85% of cohort >50 years)	up to 24 months
	High	Chang et al. [28] 1999	Clinical Trial (1993–1994)	25 M=50 (36–73)	
		Elias et al. [31] 1993	Clinical Trial (1985–1992)	19 M=49 (25–58)	up to 12 months
		Korones et al. [43] 2003	Clinical Trial NR	29 M=49 (28–76)	M=56 days (1–11 months)

Immunocompromised Population	Risk of Bias Rating	Citation Year	Study design (study years)	Study population size Age years (range)*	Length of follow up†
		Kulke et al. [44] 2006	Clinical Trial NR	29 M=56 (28–78)	Median duration of treatment was 7.3 months
		Parikh et al. [57] 2008	Prosp Cohort NR	350 NR	NR
Solid Organ Transplant (SOT)	Medium	Arness et al. [18] 2008	Retro Cohort (2001–2004)	612 M=51.6 (19.4–81.2)	≥ 2 months
		Helfrich et al. [37] 2017	Retro Cohort (2012)	360 A=52.4 (SD, ±13.0)	M=680 days
		Koo et al. [42] 2013	Retro Cohort (1995–2010)	314 M=54 (17–71)	M=4.1 years (1.0–8.1)
		Levitsky et al. [49] 2005	Retro Cohort (1993–2004)	942 M=59 (6–71)	NR
		Pergam et al. [59] 2011	Retro Cohort (1995–2007)	1077 M=53.9	A=3.8 years
		Triemer et al. [67] 2000	Retro Cohort (1993–1997)	325 A=44	6 months
		van de Beek et al. [70] 2008	Retro Cohort (1988–2006)	313 M=52 (38–59)	5.5 years
	High	Laftavi et al. [47] 2011	Retro Cohort (2001–2009)	90 <65 years: A=48	3 years
		Saber et al. [61] 2007	Retro Cohort (2000–2005)	103 A=40 (15–69)	M=13.2 months
		Stratta et al. [66] 1994	Retro Cohort (1989–1992)	82 PPX cohorts: I: A=34.5 (SEM, ±1.3) II: A=37 (SEM, ±1.1) IIIA: 35.4 (SEM, ±2) IIIB: 34.9 (SEM, ±2)	Up to 4 years

*A, average; M, median; VACV, valacyclovir; VZV, varicella zoster virus; PPX, prophylaxis

†NR, not reported; PY, person-years