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Herpes zoster incidence in a multi-center cohort of solid organ transplant recipients

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Abstract

Background—Immunosuppressed patients are at increased risk for herpes zoster (HZ), but incidence in solid organ transplant (SOT) recipients has varied in multiple studies. To assess incidence of HZ, we examined patients who underwent SOT and received follow-up care within the large multicenter Us Department of Veteran's Affairs Healthcare system.

Methods—Incident cases of HZ were determined using ICD-9 coding from administrative databases. A multivariable Cox proportional hazards model, adjusted for *a priori* risk factors, was used to assess demographic factors associated with development of HZ.

Results—Among the 1077 eligible SOT recipients, the cohort-specific incidence rate of HZ was 22.2 per 1000 patient-years (95% confidence interval [CI], 18.1–27.4). African Americans (37.6 per 1000 [95% CI, 25.0–56.6]) and heart transplants recipients (40.0 per 1000 [95% CI, 23.2–68.9]) had the highest incidence of HZ. Patients transplanted between 2005 and 2007 had the lowest incidence (15.3 per 1000 [95% CI, 8.2–28.3]). In a multivariable model, African Americans (hazard ratio [HR] 1.88; 95% CI: 1.12, 3.17) and older transplant recipients (HR 1.13; 95% CI: 1.01, 1.27 [per 5-year increment]) had increased relative hazards of HZ.

Conclusions—These data demonstrate that HZ is a common infectious complication following SOT. Future studies focused on HZ prevention are needed in this high-risk population.

Keywords

herpes zoster; infection; liver transplantation; kidney transplantation; African American

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Background

Herpes zoster (HZ) is a frequent complication of varicella zoster virus infection, and occurs with an estimated annual incidence of 1.5 to 3.0 cases per 1000 persons-years (1). Up to 20% of individuals develop HZ during their lifetime (2), and rates are increased in the elderly and in those with impaired cell-mediated immunity or underlying malignancy (1,3,4). These susceptible populations may also be at increased risk for post-herpetic neuralgia and other complications of HZ (5).

The number of solid organ transplants (SOTs) in the United States has increased over the past few decades (6,7) and improvements in immunosuppression and post-transplant management have increased allograft survival (8). Because of the need for lifetime immunosuppression, SOT recipients are at increased risk for developing HZ. However, because of variations in immunosuppressive regimens, organ transplanted, antiviral prophylaxis, and other center effects, results in single-center prevalence estimates of HZ in SOT patients vary anywhere from 1.5% –16.2% (9–16). A large multi-center study evaluating overall incidence could help to confirm findings seen at individual centers.

The US Department of Veteran's Affairs (VA) healthcare system patient population is of considerable interest, because of its large size and national representation. The VA healthcare system is the largest single-payer healthcare system in the United States (17) and vulnerable populations, such as underrepresented minorities and people with low incomes are present in substantial numbers in this population (18). The VA began offering SOTs to veterans in 1961, and currently provides access to kidney, liver, heart, pancreas, and lung transplants. We conducted a multicenter retrospective population-based cohort study using the VA's large administrative database, in order to assess the incidence of HZ in SOT recipients.

Materials and methods

Patient population

The VA has maintained electronic records on all patients treated in VA facilities for >30 years, and their database currently contains longitudinal records on all persons seeking care in >150 federal hospitals and nearly 900 outpatient clinics (17). We accessed these electronic records to identify a cohort of veterans who had undergone their first SOT at a VA-affiliated hospital between January 1995 and December 2007. Eligible patients were identified using specific transplant surgery International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) procedure codes associated with specific organ transplants (ICD-9 codes 33.5 [lung], 33.6 [combined heart lung], 37.5 [heart], 50.5 [liver], 52.8 [pancreas], and 55.6 [kidney]). Persons who survived <14 days after transplant, non-veterans, and those who underwent transplantation at non-VA facilities but who received follow-up care within the VA were excluded from all analyses.

Information on demographic factors, hospitalizations, and outpatient care were ascertained for the cohort from VA electronic medical records contained in an administrative database. Demographic information included age at transplantation, sex, race and ethnicity, and year of transplantation. Since VA transplant centers are located in Oregon, Pennsylvania, Iowa, Texas, and 2 other non-VA hospitals contracted by the VA to perform liver transplants in Virginia and Tennessee, we also assessed geographic region of VA hospital where the transplant took place (East, Midwest, South, and West). To assess other co-morbidities, we calculated an adapted Charlson index for ICD-9 coding (Charlson-Deyo) (19). This index summarizes the presence or absence of 17 medical conditions, and a score of 0 means that

none of these co-morbid conditions is present; a higher score indicates greater burden of comorbidity (20). For these analyses, this index was classified as having none, 1, 2, or ≥ 3 comorbidities (19,20). We further identified organ rejection/failure (996.8 Complications of transplantation – transplant failure or organ rejection) and cytomegalovirus (CMV) disease (078.5 Cytomegaloviral disease), as both are common transplant complications that might alter patient outcomes and were available in this administrative dataset.

Available records were also used to determine VA service connection, defined as a disability or illness that is considered a result of or aggravated by military service (21). To evaluate differences in this variable, we specified whether patients had service-connected disability (>=10% vs. < 10%). Additionally, war-time veterans can receive a pension if they are permanently and totally disabled from non-service connected disabilities and have very low income. We classified these patients as having received a pension for non-service connected disability. All others we considered to be non-service connected and without VA pension. Since patients are known to seek care outside of the VA system (22) and service connection strongly predicts the use of VA healthcare services (23), service connection can serve to adjust for VA healthcare use. In addition, service connection can be used as a proxy for socioeconomic status (24).

Outcome

An incident case of HZ was defined in patients newly linked with the ICD-9 code 053 (Herpes zoster) during either an inpatient or outpatient visit in the post-transplant period (25). If a patient developed recurrent HZ, they were only considered to have developed HZ with the primary episode in all primary analyses. Recurrent episodes of zoster were identified in patients with prior HZ who had a newly linked HZ ICD-9 code (except those associated with post-herpetic neuralgia) 180 or more days after primary diagnosis (26). We also indentified patients who developed post-herpetic neuralgia defined as the appearance of the following ICD-9 codes: 053.12 (post-herpetic trigeminal neuralgia), 053.13 (post-herpetic polyneuralgia) or 729.2 (neuralgia, neuritis, and radiculitis, unspecified) (27). These methods have been validated using the VA's large administrative dataset in prior epidemiologic studies (28–32), and have been shown to have a positive predictive value of 90% for HZ (32). Inpatient codes were available prior to January 1995, but outpatient diagnostic codes only became available beginning on October 1, 1996. In order to account for these missing data, only patients with both outpatient and inpatient data were included in these analyses.

Statistics

The incidence rates of HZ were estimated by dividing the number of incident HZ cases developed in cohort subjects by the number of years of person-time at-risk (post transplant) contributed by the overall cohort; 95% confidence intervals (CI) were estimated based on a Poisson distribution. Rates were then stratified by age at transplant, race, type of organ transplanted, and calendar year transplanted. Incidence rates were also calculated at each year post transplant by excluding patients who had developed their first episode of HZ in the prior year and including events only during the assessed post-transplant year. Cumulative incidence curves were also used to estimate incidence of HZ during follow-up, censoring at last VA contact, and considering re-transplantation and death as competing risks. Cumulative incidence curves were compared between subgroups of race, organ transplanted, and calendar year of transplant using the log-rank test.

To estimate demographic risk factors for the development of post-transplant HZ, univariate and multivariable Cox proportional hazards models were used. For analyses, available *a priori* variables included age (per 5-year interval), race (black, white, other), type of

transplant (kidney, liver, heart), transplant calendar year (modeled as a group linear term [Oct 1996–1999, 2000–2004, 2005–2007], and comorbidity index (0 to ≥3), organ rejection/failure, any CMV disease, and VA service-connection status (service connected and non-service connected). Organ rejection and CMV disease were added as time-dependent variables. Patients were censored at death, re-transplantation, or when lost to follow-up. All proportional hazards assumptions were evaluated by examining Schoenfeld residuals (33) and log-log plots of overall survival (34). All statistical analyses were completed using STATA version 10 (College Station, Texas USA). The study was approved by the University of Washington and VA Puget Sound Institutional Review Boards.

Results

We identified 1781 subjects that underwent SOT within the VA healthcare system from 1995–2007 using the VA administrative database. After exclusion of non-veterans (n=409), patients with missing outpatient data (n=205) and subjects who survived less than 14 days (n=90), a total of 1077 were eligible for analysis (Table 1). The median age at transplant for the cohort was 53.9 years (interquartile range [IQR] 48.2, 59.2). The cohort was made up primarily of men (n=1053 [98%]). The cohort was mostly white 741/1107 (69%) and African American 168/1254 (16%); there was a small number of other races (168/1254 [16%]). The majority of patients underwent a kidney (500 [46%]) or liver transplant (461 [43%]), while there were smaller numbers of those receiving heart (80 [7.4%]) and other organ transplants (36 [3.3%]). Most transplants occurred in the Southern and Eastern United States, likely reflecting the geographic distribution of transplant centers within the VA system.

In this cohort, HZ developed in 90 (8.4%) of the 1077 subjects at a median of 2.6 years (IQR 0.87, 4.50) after transplantation. The incidence rate of HZ in those transplanted after October 1996 was 22.2 per 1000 patient-years (95% CI: 18.1, 27.4) over the post-transplant follow-up period (Table 2). In those patients developing HZ, 4/90 (4%) developed at least 1 recurrent episode 180 or more days after primary diagnosis. Additionally, 23/90 (26%) developed post-herpetic neuralgia.

Incidence rates were highest in African Americans and heart transplant recipients, while Whites and liver transplant recipients had the lowest incidence rates of HZ (Table 2). Too few women were included in this cohort to calculate incidence rates based on gender, and the limited number of Asian/Pacific Islanders and Native Americans in our population prevented evaluation of incidence in these populations. Also, owing to the small number of other organ transplant types (n=44), no comment could be made on the incidence in those with other transplanted organs. Of those patients excluded in incidence assessments for lack of outpatient data, 20/205 (10%) of patients were noted to have developed HZ at some point during their follow-up.

Incidence rates were increased within age strata and declined in patients transplanted during the later calendar years of the cohort also declined (Oct 1996 –1999vs. 2005–2007). Cumulative incidence estimates indicate that patients remained at risk during the entire period follow-up (Fig. 1). As shown in Figure 2A cumulative incidence of HZ also differed by recipient race. Although heart transplants had the highest rates of HZ, no significant difference in incidence was found, based on type of organ transplanted (Fig. 2B). Additionally, no difference in cumulative incidence of HZ was found during the first 2 years post transplant, when compared between calendar years (Fig. 3).

In univariate analyses, the relative hazards of developing HZ in African American transplant recipients were higher when compared to Whites, while other races had similar relative

hazards when compared to Whites (Table 3). Other risk factors associated with HZ included organ rejection, timing of transplant (calendar year), and service connection. Patients that developed organ rejection also were at increased hazards for HZ when compared to patients who did not. The type of transplant, patient age, CMV disease, and comorbidity index did not alter the hazard of developing zoster in univariate analyses.

In the multivariable model, the relative hazards of HZ were increased in African Americans compared to Whites, and in those who were older at time of transplant (per 5-year increments) (Table 3). Subjects who were not service connected remained at lower relative hazards for HZ, as did patients transplanted in the latter calendar years of the cohort. In these multivariate analysis, organ rejection, type of organ transplanted, comorbidity index, and CMV disease did not alter hazards of HZ.

Discussion

This study demonstrates a high incidence of HZ in a large multi-center cohort of VA SOT recipients. The overall incidence in this cohort was 22.2 per 1000 patient-years, with African American subjects and heart transplant recipients demonstrating the highest incidence of post-transplant HZ. In a time-dependent model, African Americans, older transplant recipients and those with prior organ rejection also appeared to have higher rates of HZ. Subjects remained at risk throughout the entire post-transplant follow-up period.

To the best of our knowledge, this study is the largest multi-center cohort of SOT recipients to date to assess the incidence of HZ. These data provide important information on long-term risk of HZ following SOT, afford the first assessment of risk in other non-white populations, and present further evidence for an increased risk of HZ in SOT recipients. Other published studies evaluating HZ incidence in this transplant population have been limited to single centers, short follow-up periods, and or a specific type of transplant (kidney, liver, lung, and heart). Corresponding to these varied populations and study methods, the reported incidence of rates of HZ have varied from 1.5% to 16.2% (9–15). Our data are in accordance with the two largest studies published to date (9,10), which indicate incidence rates anywhere from 2–5 times those seen in the general population (35,36).

The age-related increase in HZ in older transplant recipients seen in our study is similar in magnitude to that seen in the immunocompetent population, and is likely a reflection of ongoing decline in varicella zoster virus-specific T-cell immunity, in addition to transplant-related immunosuppression (37,38). These findings are of particular public health importance. Patients aged 60 years and older represent the fastest growing population with end-stage renal disease worldwide (39). Furthermore, the number of new registrants for kidney transplants between the ages of 50 and 64 years has doubled and those aged 65 years and older has nearly tripled (39,40).

Most studies evaluating HZ incidence in SOT have focused primarily on white recipients. While large databases, such as the United Organ Network for Organ Sharing and the Scientific Registry for Transplant Recipients, would be useful for calculating population based incidence rates, they do not currently collect information on HZ. Our cohort's racial and ethnic distribution are more consistent with current US census data (41), and provide a longitudinal assessment of HZ incidence in SOT recipients in the US. In addition to assessing incidence in a more heterogeneous population then has previously been possible, the availability of follow-up data reveals important new information on the long-term rate of HZ following SOT.

This is the first study to demonstrate a higher incidence of HZ in African American SOT recipients. The increased incidence seen in African Americans in our study could be caused

in part by higher rates of organ rejection in African Americans (42–44), differences in immunosuppressive regimens (45,46) or metabolism (47–50), or as yet undetermined racial variations in viral immune response, as seen in other viral infections (51–53). The limited but conflicting findings in regards to racial differences in HZ incidence seen in other non-transplant populations (54), also suggest that these findings warrant confirmation in future studies.

Differences in health care utilization could also be a reflection of racial variations in HZ incidence, as African Americans are known to access VA services at higher rates than Whites (55,56). In addition, the overall incidence rates in our study are most likely an underestimation, as incident cases are expected to be missed in those who sought care at non-VA facilities. Finally, our finding that service connection, a reflection of VA healthcare use, was associated with an increased incidence of HZ is consistent with this hypothesis as improved access would be associated with a higher event capture. These data in African Americans may therefore be a more accurate assessment of HZ risk in SOT, and the rates described in this population will be important to consider in planning future prospective trials.

Heart transplant recipients had a high rate of HZ in our cohort, which is consistent with prior studies (10,57,58), and may be a reflection on differences in immunosuppression (59). In contrast, liver transplants are relatively resistant to rejection compared to other organs and generally require less immunosuppression (60). The lower incidence of HZ seen in liver transplant recipients in our cohort and in other studies (10,13), provides further evidence that intensity of immunosuppression may be important in determining risk of HZ. We can only hypothesize about the decline in HZ incidence in those patients transplanted in more recent years. The decreased incidence seen in latter cohorts is likely in part a result of shorter follow-up and the increasing use of antiviral prophylaxis for CMV, which has been shown to further limit risk of HZ in the first 1–2 years following transplantation (9,10,61). Improvements in immunosuppressive regimens, prevention of rejection, and other alterations in antiviral prophylaxis may also play a role in this decline, but will need to be assessed in future studies.

The high penetrance of HZ seen in this study indicates a need for future prevention studies. Current American Society of Transplantation guidelines do not recommend antiviral prophylaxis (62), and to date no formal studies of HZ prevention in SOT have been published. Because daily acyclovir is safe and has been shown to prevent the development of HZ in other immunosuppressed populations (63–65), prospective studies are needed to assess long-term antiviral drug prophylaxis after organ transplantation. Additionally, while the currently available HZ vaccine is contraindicated in SOT recipients (66), future studies are needed to address the safety and efficacy of the live-attenuated virus vaccine in the pre-transplant period. Ongoing studies using a heat-killed HZ vaccine in immunosuppressed populations may provide another option for future prevention (67).

Determining the incidence rate of HZ in SOT recipients is complicated by the diverse demographics of the population, data ascertainment from primarily outpatient records, and the inherent costs of long-term follow-up studies. The VA healthcare system database provided an efficient way to assess the incidence of HZ in large multi-center population of transplant recipients over a 10-year period. However, this analysis has strengths and limitations imposed by these data. It is probable that these data underestimate the true incidence rate in this population, as incident and recurrent cases of HZ in subjects who sought alternate clinical care outside of the VA system were not captured (68). In addition, although rates of post-herpetic neuralgia are similar to rates in other post-transplant populations (9), higher rates reported by others suggest that we may also underestimate the

frequency of this complication (10). Because of our use of ICD-9 coding, we could not assess invasive HZ complications or dissemination, both of which may be higher in SOT recipients (69). Furthermore, data on bacterial super-infection need to be assessed in future prospective studies. Most importantly, we could not address critical treatment-related risk factors, such as immunosuppressive regimen and concomitant antiviral therapy, as other studies have done (10,13). However, our data are strengthened by the size and multi-center nature of the cohort, the length of long-term follow-up, and the racial and ethnic diversity of the VA population. Furthermore, since our incidence rates are likely conservative, they could be useful for developing appropriately powered clinical trials in HZ prevention.

In summary, in this cohort of VA SOT recipients, we found that HZ was a common infectious complication in the post-transplant period. African Americans, subjects receiving heart transplants, and older transplant recipients appeared to have the highest incidence rates of HZ. In addition, in time-dependent analyses, African Americans, subjects who developed organ rejection and older transplant recipients appeared to have higher rates of HZ. The rates of HZ seen during long-term follow-up of this multi-center cohort confirm findings from other large retrospective studies, and provide additional support for future studies in HZ prevention.

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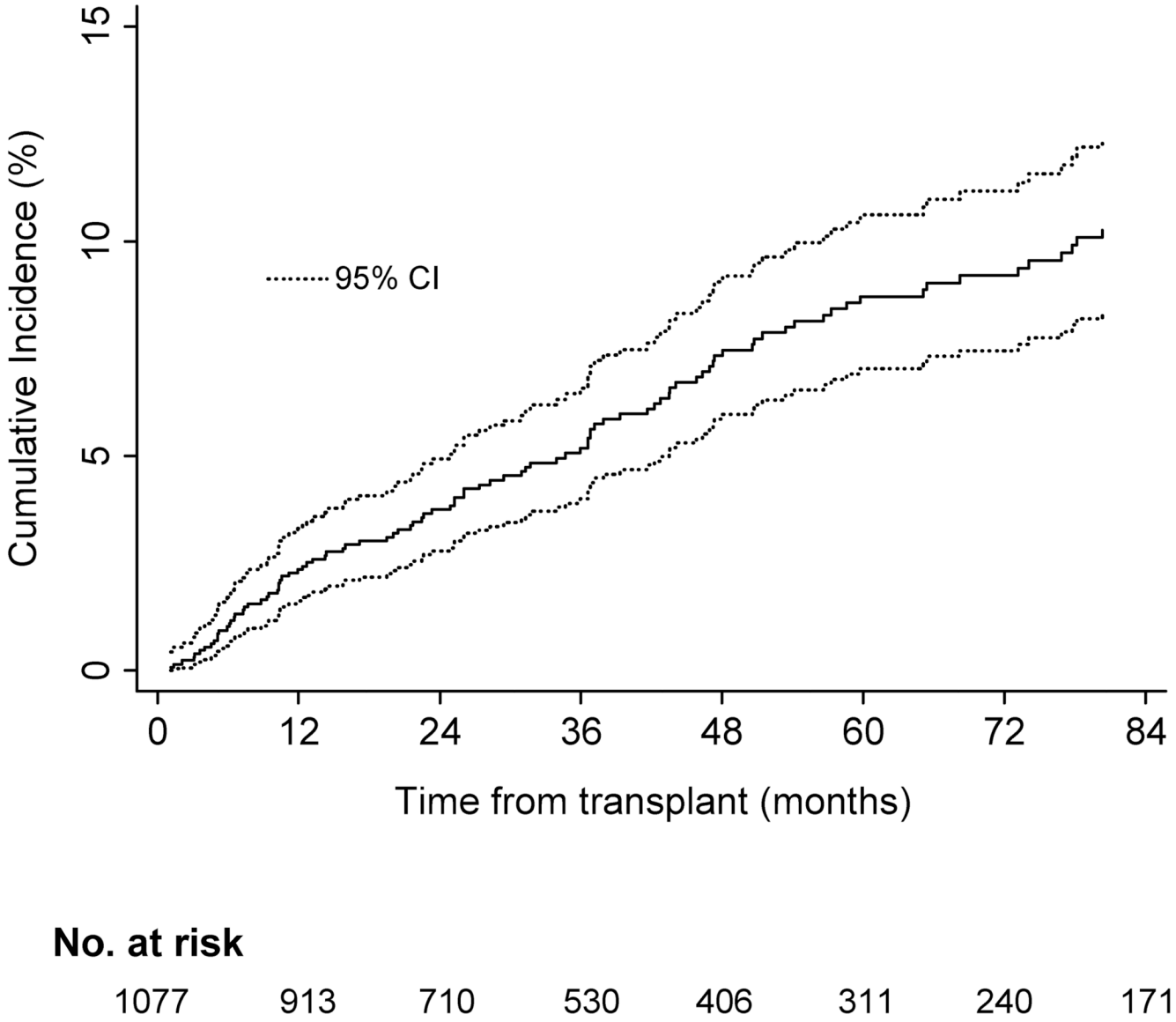

No. at risk

1077	913	710	530	406	311	240	171

Fig. 1.

Cumulative incidence of herpes zoster post transplant in cohort of VA solid organ transplant recipients from 1996–2007 (n=1077). Cumulative incidence curves censored for lost to follow-up; death and re-transplantation considered competing risks. VA, Veteran's Affairs Healthcare System; CI, confidence interval.

Figure 2a.

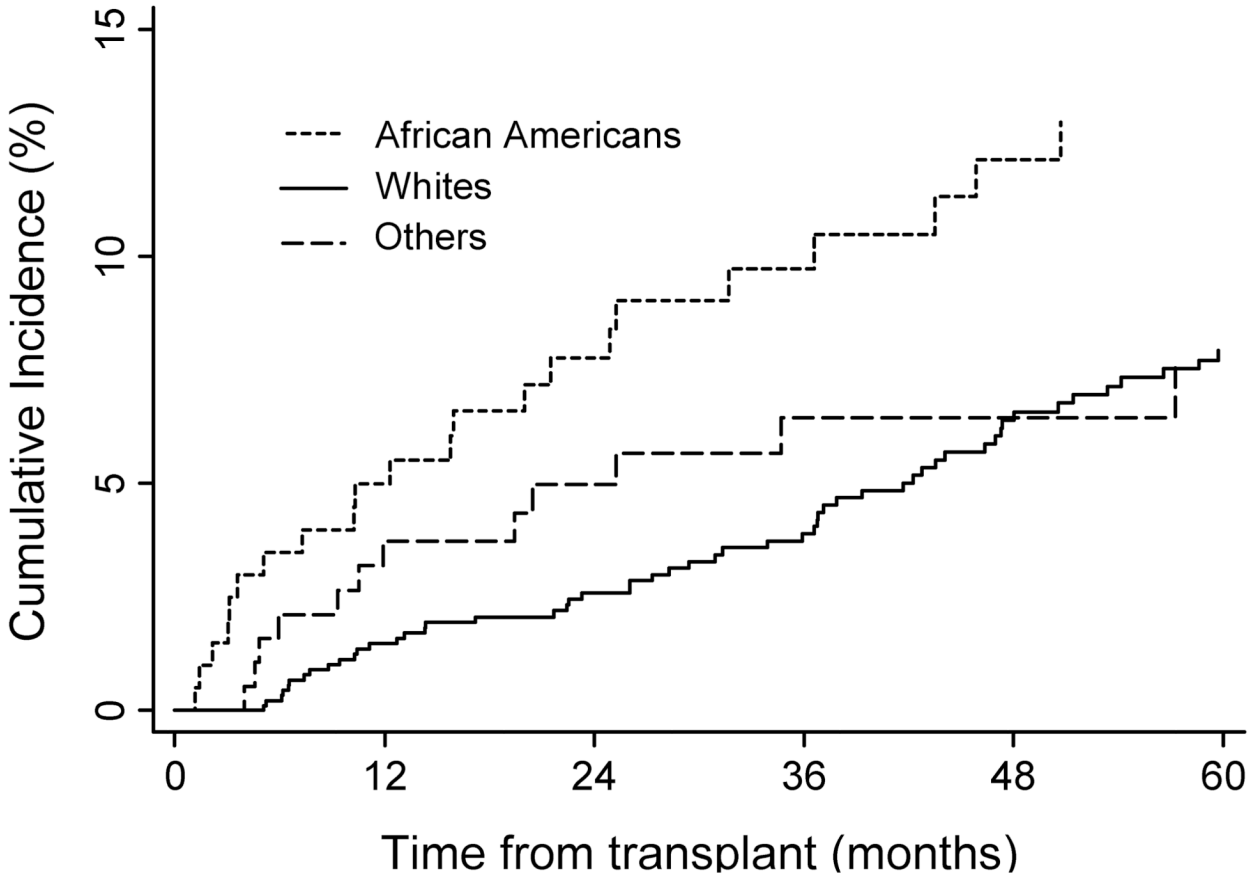

Figure 2b.

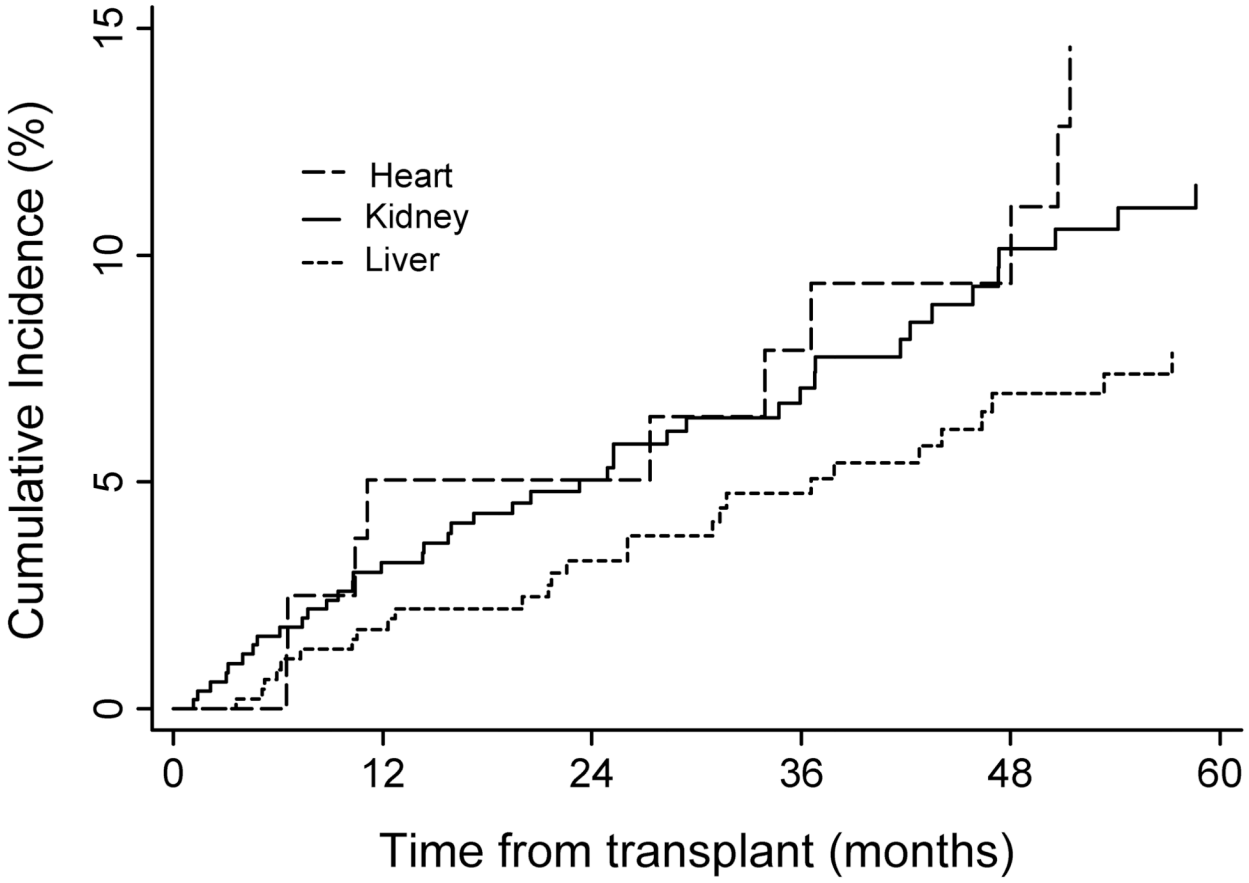

Fig. 2.

Cumulative incidence of herpes zoster post transplant in cohort of VA solid organ transplant recipients from 1996–2007 by race and organ type (n=1077). Cumulative incidence curves censored for lost to follow-up; death and re-transplantation considered competing risks. (A) Log-rank test between curves showed a significant difference between the three groups. (*P*=0.023). A log-rank test between curves for Whites and African Americans demonstrated a significant difference between the two groups (*P*=0.007) Cumulative incidence of herpes zoster by race. (B) A log-rank test between curves showed a significant difference between the three groups (*P*=0.053). Cumulative incidence of herpes zoster by organ type. VA, Veteran's Affairs Healthcare System.

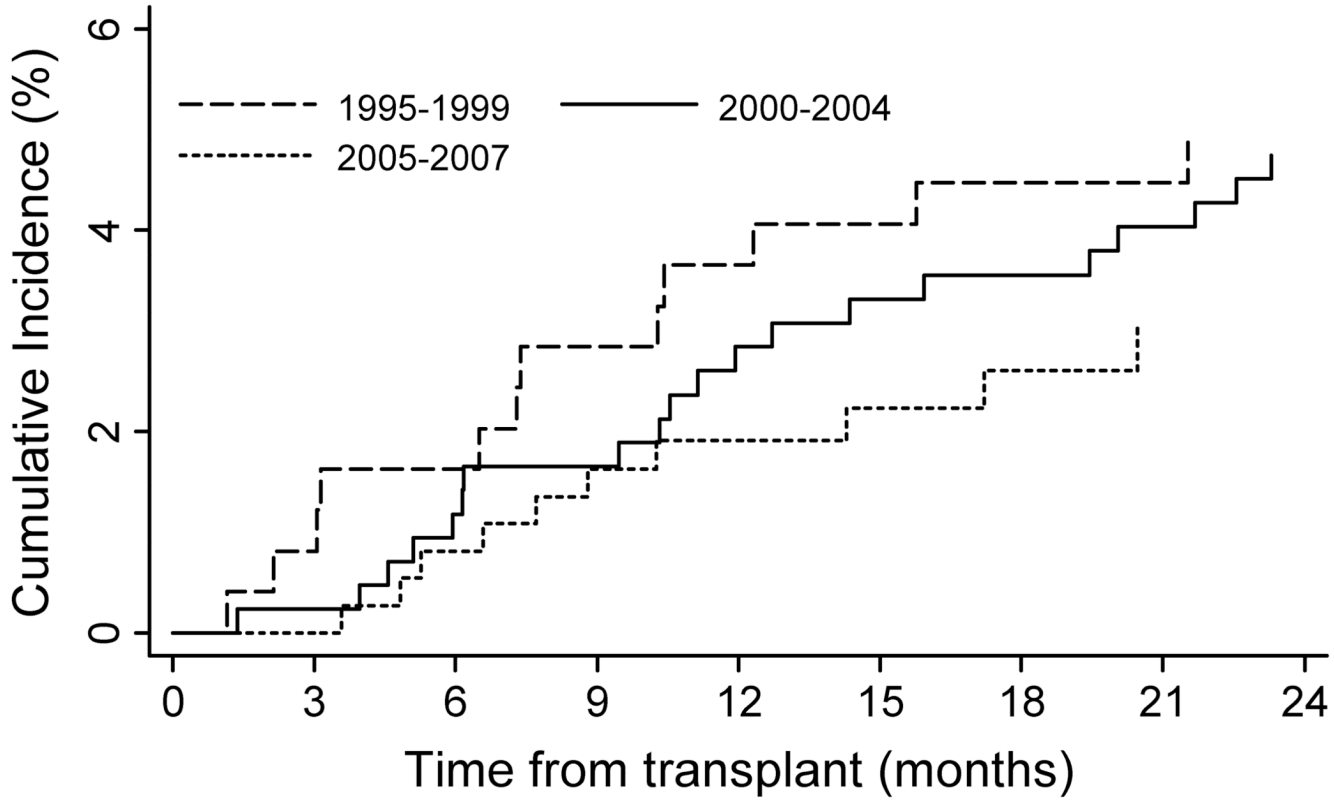

Fig. 3.

Cumulative incidence of herpes zoster during the first 2 years post transplant in a cohort of VA solid organ transplant recipients from 1996–2007 by calendar year (n=1077). Cumulative incidence curves censored for lost to follow-up; death and re-transplantation considered competing risks. A log-rank test between curves showed no difference between the three groups (*P*=0.45). VA, Veteran's Affairs Healthcare System.

Table 1

Demographics of cohort of subjects transplanted at Veteran's Health Affairs Hospitals from 1996–2007 (n=1077)

Variables	Cohort n (%)[1]
Time at risk	1372 ± 1038
Age (median [IQR])	53.9 [48.2, 59.2]
Sex (Male)	1053 (97.8)
Race/ethnicity	
White	741 (68.8)
African American	168 (15.6)
Hispanic	63 (5.9)
Asian	9 (0.8)
Native American	12 (1.1)
Other/Unknown	84 (7.8)
Transplant type	
Kidney	500 (46.4)
Liver	461 (42.8)
Heart	80 (7.4)
Others	36 (3.3)
Year of transplant	
Oct 1996–1999	261 (24.2)
2000–2004	439 (40.8)
2005–2007	377 (35.0)
Comorbidity index[2]	
0	136 (12.6)
1	155 (14.4)
2	270 (25.1)
≥3	516 (47.9)
VA status	
Service connected ≥10%	377 (35.0)
Service connected <10%	23 (2.1)
No service connection	548 (50.9)
Pension	129 (12.0)
Geographic region	
West	254 (23.6)
Midwest	114 (10.6)
South	373 (34.6)
East	336 (31.2)
Organ rejection[3]	
Yes	528 (49.0)
No	549 (51.0)

Variables	Cohort n (%)[1]
CMV[3, 4]	
Yes	107 (9.9)
No	970 (90.1)

[1] Because of rounding, percentages may not equal 100.

[2] Adapted Charlson Index.

[3] Before development of herpes zoster.

[4] Any CMV event.

VA, US Department of Veteran's Affairs healthcare system; IQR, Interquartile range; CMV, cytomegalovirus.

Table 2

Incidence rates of herpes zoster in cohort of solid organ transplant recipient Veterans from October 1, 1996–2007 (n=1077)[1]

Variable	n	Person-years at risk	Cases	IncidencerRate[2] (95% CI)
Overall	1077	4044	90	22.2 (18.1, 27.4)
Age				
<45	161	784	16	20.4 (12.5, 33.3)
45 – 55	446	1815	36	19.8 (14.3, 27.5)
55+	470	1445	38	26.3 (19.1, 36.1)
Race				
White	741	2831	55	19.4 (14.9, 25.3)
African American	168	612	23	37.6 (25.0, 56.6)
Other	168	601	12	20.0 (11.3, 35.1)
Type of transplant				
Kidney	500	1847	45	24.4 (18.2, 32.6)
Liver	461	1751	32	18.3 (12.9, 25.8)
Heart	80	325	13	40.0 (23.2, 68.9)
Year of transplant				
1996–1999[3]	261	1553	45	29.0 (21.6, 38.8)
2000–2004	439	1835	35	19.1 (13.7, 26.6)
2005–2007	377	657	10	15.2 (8.2, 28.3)
Year post transplant				
Year 1	1077	996	28	28.1 (19.4, 40.7)
Year 2	913	812	14	17.2 (10.2, 29.1)
Year 3	710	615	14	22.8 (13.5, 38.4)
Year 4	530	464	15	32.3 (19.5, 53.6)

[1] Excludes patients with survival ≤14 days and those with incomplete outpatient data.

[2] Per 1,000 patient-years.

[3] Patients only after October 1996.

CI, confidence interval.

Table 3

Cox proportional-hazard models for the development of herpes zoster in solid organ transplant recipients 1996 – 2007 (n=1077)

Variable	Univariate HR (95% CI)	Multivariable HR (95% CI)
Age (per 5 yrs)	1.03 (0.92, 1.15)	1.13 (1.01, 1.27)
Race		
White	1.0 (referent)	- -
African American	1.92 (1.18, 3.13)	1.88 (1.12, 3.17)
Other	1.00 (0.54, 1.88)	1.17 (0.62, 2.21)
Type of transplant		
Kidney	1.0 (referent)	- -
Liver	0.77 (0.49, 1.21)	1.08 (0.62, 1.89)
Heart	1.69 (0.91, 3.13)	1.70 (0.87, 3.34)
Transplant year[1]	0.60 (0.43, 0.83)	0.57 (0.40, 0.80)
VA status		
Service connected	1.0 (referent)	- -
Non-service connected	0.57 (0.38, 0.86)	0.51 (0.33, 0.80)
Comorbidity Index[2]		
0	1.60 (0.89, 2.88)	1.28 (0.65, 2.52)
1	1.07 (0.55, 2.07)	1.01 (0.51, 1.98)
2	1.50 (0.91, 2.49)	1.42 (0.81, 2.51)
≥3	1.0 (referent)	- -
Organ rejection[3]		
No	1.0 (referent)	- -
Yes	1.61 (1.04, 2.51)	1.42 (0.91, 2.23)
CMV[3]		
No	1.0 (referent)	- -
Yes	1.57 (0.83, 2.95)	1.34 (0.70, 2.54)

[1] Modeled as group linear term.

[2] Charlson-Deyo Index.

[3] Time-dependent variable in multivariable model.

HR, hazard ratio; CI, confidence interval; VA, US Department of Veteran's Affairs healthcare system; CMV, cytomegalovirus.