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Risk of Kaposi sarcoma after solid organ transplantation in the United States

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Abstract

Due to treatment with immunosuppressive medications, solid organ transplant recipients have elevated risk for Kaposi sarcoma (KS), which is caused by human herpesvirus 8 (HHV8). Other risk factors for KS are poorly understood. We linked the United States solid organ transplant registry with 17 population-based cancer registries to ascertain KS incidence among 244,964 transplant recipients from 1987–2014. To compare incidence rates of KS according to patient and transplant characteristics, we calculated incidence rate ratios (IRRs) using Poisson regression. To compare associations of KS with other skin cancers occurring before or within 12 months of KS diagnosis, we computed odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression. All statistical tests were two-sided. We identified 163 KS cases during follow-up. Among transplant recipients, we found significantly increased risk of KS associated with male sex (IRR = 1.87; 95%CI:1.32,2.71), nonwhite race (IRR = 2.67; 95%CI:1.92,3.72), non-US citizenship (IRR = 2.10; 95%CI:1.19,3.47), lung transplant (IRR = 2.22; 95%CI:1.03,4.24, vs. kidney), and older age at transplant. KS risk decreased significantly with time since transplant and recent calendar year, however, no specific induction or maintenance medication was associated with KS. KS incidence was not significantly associated with ambient ultraviolet radiation (IRR = 1.32 95%CI:0.87,2.02, tertile 3 vs. 1). KS incidence has decreased in recent calendar years. In a cross-sectional sample, we found cutaneous squamous cell carcinoma was associated with KS (OR = 4.83; 95%CI:1.30,14.69). KS risk factors included those potentially associated with HHV8 infection and increased immunosuppression. Our findings suggest that transplant recipients with a non-KS skin cancer may also be at high KS risk.

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Keywords

Kaposi sarcoma; human herpesvirus 8; HHV8; solid organ transplant; ultraviolet radiation; basal cell carcinoma; squamous cell carcinoma; melanoma; mTOR inhibitor; corticosteroid

Introduction

Kaposi sarcoma (KS) is a cutaneous malignancy of blood or lymphatic endothelial origin, caused by human herpesvirus 8 (HHV8, also known as KS-associated herpesvirus). Due to treatment with immunosuppressive medications, solid organ transplant recipients are at especially elevated risk for cancers caused by oncogenic viruses,[1–3] and KS incidence among solid organ transplant recipients is about 60 times higher than in the general population.[1] While infection with HHV8 usually predates the transplant, HHV8 can also be transmitted through the donor organ.[4]

Apart from severe immunosuppression associated with organ transplantation or human immunodeficiency virus (HIV) infection,[3,5] few risk factors have been firmly established for KS. Internationally, KS incidence varies notably due to large differences in the prevalence of HHV8 infection. Recently, increased risk of KS has been associated with higher ambient ultraviolet radiation (UVR) and history of cutaneous basal or squamous cell carcinoma (referred to collectively as “keratinocyte carcinomas”) among HIV-infected men.[6] Transplant recipients have a very high risk of keratinocyte carcinoma,[7–9] but the association of ambient UVR or non-KS skin cancers with KS risk has not been assessed among transplant recipients. While use of immunosuppressive medications is associated with increased risk of KS, to our knowledge, prospective data on specific immunosuppressive medications and trends in KS risk are limited. Incidence of KS in the United States (US) transplant population has been most recently examined using follow-up of patients from transplant registries between 1993 and 2003 with the outcome of KS being ascertained through reports from transplant centers.[10] That study found KS risk was increased for males, older age at transplant, HLA-B mismatch, nonwhite race, and non-US citizenship. However, transplant center reports of cancer diagnoses are likely incomplete,[11] and recent trends of KS in the US transplant population are not known.

Here we evaluate the association between demographic, environmental and treatment-related factors and risk of KS among solid organ transplant recipients in the US. We use the transplant cancer match (TCM) study which is a large population-based linkage of the US transplant registry with 17 state or regional cancer registries between 1987 and 2014. Analyses in the current study make use of 17 additional years of follow-up beyond what was previously evaluated (including data from 1987 to 1992 and 2004 to 2014), ascertain KS cases using cancer registry information, which has been demonstrated to have more complete cancer ascertainment,[11] and include linkage of residential locations to ambient UVR satellite-based data.

Materials and Methods

Overview

The TCM study (http://transplantmatch.cancer.gov) has been previously described in detail.[1] Briefly, computer-based linkages were performed between the Scientific registry of transplant recipients (SRTR) and 17 US central cancer registries (see Table 1 footnote). The SRTR includes structured data regarding all US solid organ transplants since 1987. KS cases were identified from linked cancer registry data (International Classification of Diseases for Oncology, third edition [ICD-O-3] morphology code 9140). The TCM Study was approved by human subjects' research review committees at the National Cancer Institute and (as required) participating cancer registries.

Study population

The underlying cohort included 291,373 solid organ transplants performed from 1987 to 2014 with residential location of transplant recipients known to be within the regions covered by 17 US central cancer registries. We successively excluded transplants with cancer registry coverage initiating after transplant (n = 6,155), a history of KS prior to transplant (n = 26), persons with known HIV infection at time of transplant (n = 526), transplants in persons aged <15 years at transplant (n = 16,146, among whom there were zero KS cases), and persons with poorly specified residential location (n = 3,896, with 2 KS cases). The main study sample included 264,624 transplants (244,964 unique individuals). Follow-up began at time of transplant and ended at the earliest of KS diagnosis, death, failure of a transplanted organ, subsequent transplant, first loss to follow-up by the SRTR or end of cancer registry coverage. Most factors were examined in relation to incidence of KS using this cohort.

Many KS cases were diagnosed soon after transplantation, allowing for little prospective follow-up time to ascertain non-KS skin cancers (e.g., basal cell carcinoma, cutaneous squamous cell carcinoma, and melanoma). We therefore examined the cross-sectional relationship of non-KS skin cancers and KS by creating a case–control sample nested within this primary study population. Controls must have been alive and free of KS at the follow-up time (representing time since transplant) of diagnosis of the index case. We matched each KS case (n = 163) with 20 control transplant recipients on sex, transplanted organ, age at transplant (±2 years), and calendar year of transplant (±2 years).[12] We restricted this analysis to non-Hispanic whites because non-KS skin cancers are rare among nonwhites and none occurred among non-white KS cases. Non-KS skin cancers were included if they occurred before or within 12 months after KS diagnosis for the case and the equivalent follow-up time for the controls in that set.

Exposure assessment

Baseline information on recipient demographic characteristics and immunosuppressive medications prescribed at the time of transplant was obtained from the SRTR. The SRTR also provided information on diagnoses of basal or squamous cell carcinoma during posttransplant follow-up, because these malignancies are not ascertained by cancer

registries. Diagnoses of melanoma prior to transplant as well as during posttransplant follow-up were obtained using the linked cancer registry data.

Average annual ambient UVR exposure for transplant recipients was derived by linking their zip code of residence at the time of transplantation or listing, to the Total Ozone Mapping Spectrometer database maintained by the National Aeronautics and Space Administration.[13] Cloud-adjusted daily ambient ultraviolet irradiance at 305 nm, which is part of the UVB spectrum, is provided on a 1° latitude by 1° longitude grid corresponding to approximately 111 by 85 km, respectively. Daily noontime satellite-based estimates were averaged over years 1982–1992 to account for any annual fluctuations due to the 11-year solar cycle.[14] Tertile cutoffs for ambient UVR (6.0–26.4, 26.5–43.1, 43.2–84.0 mW/m^2) were based on the UVR distribution among eligible subjects.

Statistical analysis

To evaluate the relationship of baseline recipient risk factors with KS incidence, we used Poisson regression to calculate incidence rate ratios (IRRs). Demographics and characteristics of the transplanted organs were assessed in a multivariable model that included sex, age at transplant, race (white, nonwhite), US citizenship, transplanted organ (kidney, liver, heart, lung, other/multiple), calendar year of transplant and a time-dependent variable for time since transplant. Poisson regression was also used to examine the associations between incident KS and ambient UVR and induction and maintenance medications after adjusting for sex, age at transplant, race, US citizenship, calendar year of transplant and time since transplant. Induction and maintenance medications were tested as potential effect modifiers of the ambient UVR dose–response. *p*-values for trend, heterogeneity and interaction were based on likelihood ratio tests. Poisson regression analyses were conducted using the AMFIT module of Epicure (RSI, Ottowa, Canada).[15] To examine the association between non-KS skin cancers with KS risk using nested case–control data, we conducted conditional logistic regression to calculate matched odds ratios (ORs) and due to small numbers, provided exact *p*-values and confidence intervals (CIs) using SAS software (version 9.3, SAS Institute, Cary, NC). All statistical tests were two-sided and *p* values less than 0.05 were considered significant.

Results

The study population included 264,624 transplants (Table 1) with 1,310,880 person-years of follow-up. Sixty-two percent of transplant recipients were male, and the median age at transplant was 50 years. Non-Hispanic whites represented 62% of transplants and US citizens represented 96% of transplants. Most transplants were kidney (59%), followed by transplants of the liver, heart and lung.

KS incidence was 87% higher in men than women, over twofold greater in nonwhites than whites and twofold higher in non-US citizens than US citizens. There were 163 KS cases identified during follow-up (Table 2). KS incidence increased with age at transplant and decreased sharply with time since transplant, so that the highest incidence occurred within 1 year of transplant. Lung recipients had the highest incidence of KS when compared to kidney transplants, although there was no overall heterogeneity in KS risk across organ types

(p = 0.23). KS incidence decreased significantly with increasing calendar year of transplant surgery.

We examined risk of KS in relation to ambient UVR and non-KS skin cancers (Table 3). Compared with the lowest ambient UVR tertile, KS incidence was not significantly elevated in the highest tertile, either in the total population (IRR = 1.32; 95% CI: 0.87, 2.02) or among non-Hispanic whites (IRR = 1.18; 95% CI: 0.64, 2.20). In contrast, among non-Hispanic whites, KS was significantly associated with diagnosis of cutaneous squamous cell carcinoma (odds ratio [OR] = 4.83; 95% CI: 1.30, 14.7), but not significantly elevated with basal cell carcinoma (OR = 2.95; 95% CI: 0.55, 10.3) or melanoma (OR = 10.00; 95% CI: 0.17, 192.1).

We did not find any induction or maintenance medication to be significantly associated with KS risk (Table 4). However, KS incidence was marginally increased in association with corticosteroid use (IRR = 1.59; 95% CI: 0.93, 2.79). Medication use did not significantly modify the relationship between ambient UVR and KS (data not shown).

Discussion

In this large, population-based cohort study of solid organ transplant recipients with information on demographic and transplant characteristics, medication use and diagnosed medical conditions, spanning 27 calendar years, KS risk was significantly higher for factors potentially associated with HHV8 infection and greater immunosuppression. This is the first study to examine the associations of ambient UVR and skin cancers with KS risk in the transplant population, and we observed a significant association with squamous cell carcinoma of the skin. Our study is also the first to report a decrease in KS incidence for more recent solid organ transplant recipients.

Some factors associated with increased KS risk in our study likely reflect differences in HHV8 prevalence. Prevalence of HHV8 is low (<2%) in the general US population,[16,17] however several factors are related to higher prevalence of HHV8 among adults, including older age and, among men, coinfection with other viruses (hepatitis B and herpes simplex virus) and engaging in sexual activity with other men.[16] Consistent with our finding of an elevated incidence of KS among transplant recipients of non-US citizenship, the prevalence of HHV8 is especially high in some other countries, including in sub-Saharan Africa and countries along the Mediterranean.[17]

KS risk was not related to ambient UVR in this transplant population. In contrast, we recently found a significantly increased risk of KS with high ambient UVR in a population of HIV-infected men.[6] Since all subjects had HIV in that study, and because HIV and HHV8 infection often co-occur in the same groups (e.g., men who have sex with men [MSM]), the associations with ambient UVR were somewhat protected from confounding by geographic differences in HHV8 prevalence. In contrast, in this transplant population, KS cases tended to occur in urban areas (data not shown) with potentially higher rates of HIV and large populations of MSM. Although transplant recipients diagnosed with HIV were excluded, we did not have information on MSM status.

We considered the co-occurrence of other UVR-related skin cancers as possible surrogates of individual sun exposure and sensitivity because common skin cancers have well-established relationships with history of personal UVR exposure.[18–21] Although based on small numbers, we found that KS risk was significantly higher in transplant recipients with diagnosis of squamous cell carcinoma. Notably, this finding supports our previous finding of increased KS risk in HIV-infected men with non-KS skin cancers[6] and several case studies reported in the literature.[22–25] Rather than being explained by UVR, our findings may instead be explained by drug-induced immunosuppression causing both KS and non-KS skin cancers in the same people. However, these associations were seen despite adjustment through matching on factors related to immunosuppression (age at transplant, calendar year of transplant, and time since transplant). Another explanation is that patients diagnosed with either KS or a non-KS skin cancer may have increased medical surveillance for skin cancers. A limitation to this analysis is that basal and squamous cell carcinomas were ascertained through the SRTR, rather than the cancer registries. Diagnoses of these skin cancers in the SRTR have low sensitivity, but high positive predictive value.[26] Under-ascertainment of BCC and SCCs may bias effect estimates towards the null.

In this transplant population, as in others,[10,27] KS incidence peaked within 1 year of transplant, likely reflecting the effect of intensive immunosuppression prescribed in the first months after transplant. In addition, the association of KS with lung transplant may be due to particularly strong immunosuppression in this group.[28] Consistent with an earlier study in this population,[10] no specific induction or maintenance medications were significantly associated with KS risk. However, incidence of KS tended to be higher among people prescribed corticosteroids, a finding that has been observed in both epidemiological studies[29,30] and clinical settings outside of transplantation.[31–34] KS risk was not significantly decreased with prescription of mammalian target of rapamycin (mTOR) inhibitors. Some clinical studies have shown promising effects for treatment of KS using mTOR inhibitors,[35,36] possibly through a reduction in the secretion of vascular endothelial growth factor and inhibition of angiogenesis.[37] However, there are few epidemiological data on mTOR use in relation to incidence of KS.[38,39] While our findings do not support a protective role for mTOR inhibitors, they are based on small numbers and we lacked information on dose or duration. In addition, medication use was assessed only at baseline, and not updated during follow-up. If medications were commonly switched, lack of updated data may bias the associations between medication use and KS toward the null. However, this may have less impact on incidence of KS than other post-transplant malignancies, because KS usually occurred within 36 months of transplant.

In this analysis of KS among US transplant recipients, which included follow-up over 27 calendar years, we found a significant decline in KS incidence over time. Two recent nationwide population-based studies based in northern Europe have had too few cases to examine longitudinal trends of KS in the transplant population.[40,41] The decrease in KS risk over calendar time we observed may reflect improvements in management of patients such as optimized dosing of immunosuppressing medications.

Our study has several limitations beyond those mentioned above. Because we did not have data on HHV8 prevalence, the population at risk of KS is overestimated and our ability to

differentiate a risk factor for HHV8 *versus* the development of KS in a person with HHV8 infection is hampered. Another limitation is lack of information on personal sun exposure behaviors (e.g., time spent outdoors and number of episodes of sunburn). Our ambient UVR measure is based only on residence at time of transplant and may also be subject to potential confounding by factors that vary geographically such as HHV8 prevalence, which may depend on sexual and drug using behaviors and socioeconomic status. Strengths include US transplant population representativeness, follow-up over a period of 27 years, and outcome ascertainment through cancer registry linkage. Although cancer registries have been shown to be more complete than the SRTR in ascertaining cancer cases,[11] they may still miss a proportion of KS cases, resulting in effect estimates possibly biased toward the null.

In this large population-based United States study of solid organ transplant recipients, factors potentially associated with HHV8 infection or greater immunosuppression were associated with increased risk of KS. While no specific medications, including mTOR inhibitors, were significantly associated with subsequent risk of KS, recent transplant recipients had reduced KS risk suggesting possible improvements in drug prescribing patterns. Our findings also suggest that transplant recipients with non-KS skin cancers may constitute an additional high-risk group for KS and underscore the need for skin cancer screening in this population.

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What's new?

Due to treatment with immunosuppressive medications, solid organ transplant recipients are at elevated risk for cancers caused by oncogenic viruses, such as Kaposi sarcoma (KS). In this large population-based study of transplant recipients, factors potentially linked to HHV8 infection or greater immunosuppression were associated with increased KS risk. While no specific medications were significantly associated with KS risk, recent transplant recipients had reduced KS risk, suggesting possible improvements in drug-prescribing patterns. The findings also suggest that transplant recipients with non-KS skin cancers may constitute an additional high-risk group for KS, underscoring the need for skin cancer screening in this population.

Table 1.

Characteristics of solid organ transplants in the United States evaluated for risk of Kaposi sarcoma

Characteristic	No. of transplants	Percent
Total	264,624	100.0
Sex		
Female	101,066	38.2
Male	163,558	61.8
Age at transplant, years		
15 to 34	46,773	17.7
35 to 49	83,467	31.5
50 to 64	106,345	40.2
65+	28,039	10.6
Race/ethnicity		
Non-Hispanic white	164,598	62.2
Non-Hispanic black	45,826	17.3
Hispanic	37,994	14.4
Asian/Pacific Islander	14,568	5.5
Other/Unknown	1,638	0.6
Citizenship		
United States citizen	252,911	95.6
Non-United States citizen	11,713	4.4
Transplanted organ		
Kidney	157,105	59.4
Liver	55,502	21.0
Heart	23,158	8.8
Lung	12,501	4.7
Other or multiple	16,358	6.2
Calendar year of transplantation		
1987 to 1996	53,817	20.3
1997 to 2003	74,885	28.3
2004 to 2014	135,922	51.4

Data derived from the United States Scientific Registry of Transplant Recipients and 17 United States cancer registries include California (years of cancer registration 1988–2012), Colorado (1988–2009), Connecticut (1973–2009), Florida (1981–2009), Georgia (1995–2010), Hawaii (1973–2007), Illinois (1986–2013), Iowa (1973–2009), Kentucky (1995–2011), Michigan (1985–2009), New Jersey (1979–2010), New York (1976–2010), North Carolina (1990–2010), Pennsylvania (1987–2013), Seattle, Washington (1974–2014), Texas (1995–2010), and Utah (1973–2008).

Table 2.

Risk of Kaposi sarcoma in relation to demographic characteristics, transplanted organ, and time since transplant

Characteristic	KS patients	Incidence rate, per 100,000 person-years	IRR (95% CI)[1]	*p*-value[1]
Total	163	12.4		
Sex				
Female	41	8.0	Ref.	
Male	122	15.3	1.87 (1.32, 2.71)	< 0.001
Race				
White	73	8.6	Ref.	
Non-white	90	19.7	2.67 (1.92, 3.72)	< 0.001
Citizenship				
United States citizen	147	11.7	Ref.	
Non-United States citizen	16	30.1	2.10 (1.19, 3.47)	0.01
Age at transplant, years				
15–34	14	5.7	Ref.	
35–49	35	7.7	1.47 (0.80, 2.82)	
50–64	83	16.4	3.26 (1.89, 6.04)	
65+	31	28.6	6.24 (3.34, 12.25)	$P_{trend} < 0.001$
Time since transplant, years				
<1	81	35.1	Ref.	
1 to <3	57	15.6	0.44 (0.31, 0.61)	
3 to <5	13	5.0	0.13 (0.07, 0.23)	
≥5	12	2.6	0.06 (0.03, 0.11)	$P_{trend} < 0.001$
Transplanted organ				
Kidney	91	11.7	Ref.	
Liver	35	12.7	1.25 (0.83, 1.84)	
Heart	22	16.2	1.40 (0.85, 2.23)	
Lung	9	19.6	2.22 (1.03, 4.24)	
Other or multiple	6	8.1	1.26 (0.49, 2.67)	0.23
Calendar year of transplant				
1987–1996	54	14.2	Ref.	

Characteristic	KS patients	Incidence rate, per 100,000 person-years	IRR (95% CI)[1]	*p*-value[1]
1997–2003	66	13.8	0.73 (0.51, 1.06)	
2004–2014	43	9.6	0.26 (0.17, 0.39)	$p_{trend} < 0.001$

Abbreviations: KS, Kaposi sarcoma; IRR, incidence rate ratio; CI, confidence interval.

[1] Adjusted for all factors (as categorized) in the table. P-trend based likelihood ratio tests treating ordinal categories as numeric in Poisson regression.

Table 3.

Risk of Kaposi sarcoma in relation to ambient ultraviolet radiation and diagnosis of skin cancer among solid organ transplant recipients

Factor	KS patients	Incidence rate, per 100,000 person-years	IRR (95% CI)[1]	*p*-trend[1]
Total population				
Ambient UVR tertiles				
T1 (6.0–26.4 mW/m^2)	36	8.9	Ref.	
T2 (26.5–43.1 mW/m^2)	63	12.5	1.26 (0.84, 1.92)	
T3 (43.2–84 mW/m^2)	64	16.0	1.32 (0.87, 2.02)	0.22
Non-Hispanic white transplant recipients				
Ambient UVR tertiles				
T1 (6.0–26.4 mW/m^2)	21	6.6	Ref.	
T2 (26.5–43.1 mW/m^2)	32	10.0	1.53 (0.89, 2.69)	
T3 (43.2–84 mW/m^2)	20	9.3	1.18 (0.64, 2.20)	> 0.50
Skin cancer [2]	**KS cases**	**Controls**	**OR (95% CI)** [3]	***p*-value** [3]
Squamous cell carcinoma				
No	68	1,435	Ref.	
Yes	5	25	4.83 (1.30, 14.69)	0.02
Basal cell carcinoma				
No	70	1,439	Ref.	
Yes	3	21	2.95 (0.55, 10.32)	0.20
Melanoma				
No	72	1,458	Ref.	
Yes	1	2	10.00 (0.17, 192.09)	0.27

Abbreviations: KS, Kaposi sarcoma; IRR, incidence rate ratio; CI, confidence interval; UVR, ultraviolet radiation; T, tertile; OR, odds ratio.

[1] Incidence rate ratios based on Poisson regression after adjustment on sex, race, US citizenship, age at transplant (years), calendar year of transplant, and time since transplant (years). p-trend based likelihood ratio tests treating ordinal UVR categories (1–3) as numeric in regression.

[2] Diagnoses of squamous and basal cell carcinoma were ascertained by the Scientific Registry of Transplant Recipients, while ascertainment of melanoma was based on cancer registry linkages.

[3] Odds ratios based on conditional logistic regression with 20 controls matched to each Kaposi sarcoma case on sex, transplanted organ, age at transplant (±2 years), and calendar year of transplant (±2 years). Restricted to non-Hispanic white transplant recipients. Confidence intervals and p-values based on exact methods.

Table 4.

Risk of Kaposi sarcoma in relation to induction and maintenance medications prescribed at time of organ transplant

Medication	KS patients	Incidence rate, per 100,000 person-years	IRR (95% CI)[1]	*p*-value[1]
Induction medications				
Monoclonal antibodies				
No	154	12.5	Ref.	
Yes	9	11.7	0.87 (0.41, 1.62)	> 0.50
Polyclonal antibody				
No	138	12.9	Ref.	
Yes	25	10.4	0.82 (0.52, 1.25)	0.37
IL2 receptor antagonist				
No	132	12.0	Ref.	
Yes	31	14.4	1.41 (0.91, 2.12)	0.12
Baseline maintenance medications				
Cyclosporine				
No	89	11.9	Ref.	
Yes	74	13.2	0.81 (0.55, 1.19)	0.28
Tacrolimus				
No	95	14.0	Ref.	
Yes	68	10.6	0.95 (0.65, 1.40)	> 0.50
Azathioprine				
No	121	12.0	Ref.	
Yes	42	13.8	0.86 (0.55, 1.31)	0.48
MMF				
No	85	14.1	Ref.	
Yes	78	11.0	0.90 (0.61, 1.34)	> 0.50
mTOR inhibitors				
No	156	12.6	Ref.	
Yes	7	10.3	0.90 (0.38, 1.80)	> 0.50
Corticosteroids				
No	13	7.8	Ref.	

Medication	KS patients	Incidence rate, per 100,000 person-years	IRR (95% CI)[1]	*p*-value[1]
Yes	150	13.1	1.59 (0.93, 2.79)	0.09
Maintenance medication regimen				
Tacrolimus and MMF	41	9.1	Ref.	
Cyclosporine and azathioprine	34	12.9	1.01 (0.55, 1.87)	
Other	88	14.7	1.42 (0.94, 2.19)	0.08

Abbreviations: IRR, incidence rate ratio; CI, confidence interval; IL2, interleukin 2; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin.

[1]Adjusted for sex, race, US citizenship, age at transplant (years), calendar year of transplant, and time since transplant (years).