



ORIGINAL ARTICLE

Cancer incidence and risk factors in dialysis patients with human immunodeficiency virus: a cohort study

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ABSTRACT

Background. Patients with human immunodeficiency virus (HIV) or end-stage renal disease receiving dialysis have an increased risk of developing malignancies, but few data are available on cancer in patients with both conditions. Thus, the objective of this study was to determine the incidence of selected malignancies and identify their potential risk factors in HIV-infected dialysis patients.

Methods. This study was a nationwide cohort analysis using the US Renal Data System. Participants included all HIV-infected patients starting dialysis from 2005 to 2011. HIV status, comorbidities and malignancies were identified using International Classification of Diseases, Ninth Revision codes. Descriptive statistics and generalized linear models quantifying risk factors were performed for the overall cohort and the three most common malignancies.

Results. Overall, 6641 HIV-infected dialysis patients were identified, with 543 (8.2%) carrying a malignancy diagnosis. The most common malignancies were non-Hodgkin's lymphoma (NHL, 25%), Kaposi sarcoma (KS, 16%) and colorectal cancer (13%). Factors increasing the risk of any malignancy diagnosis included: history of cancer [adjusted relative risk (aRR) = 5.37], two or more acquired immunodeficiency syndrome-defining opportunistic infections (ADOIs) (aRR = 3.11), one ADOI (aRR = 2.23), cirrhosis (aRR = 2.20), male sex (aRR = 1.54) and hepatitis B (aRR = 1.52). For NHL and colorectal cancer, history of cancer (aRR = 7.05 and 9.80, respectively) was the most significant risk factor. For KS, two or more ADOIs (aRR = 6.78) was the largest risk factor.

Conclusions. Over 8% of HIV-infected dialysis patients developed a malignancy. History of cancer and ADOIs were major risk factors, underscoring the significance of immune dysregulation in malignancy development.

Keywords: cancer, chronic kidney disease, dialysis, epidemiology, ESRD, HIV, risk factors, US Renal Data System

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INTRODUCTION

Human immunodeficiency virus (HIV) is among the most significant chronic viral infections in the USA, with ~1.1 million individuals affected [1]. HIV infection leads to immunosuppression, culminating in acquired immunodeficiency syndrome (AIDS) if untreated. Even with effective treatment, chronic inflammation and immune dysregulation may persist. People infected with HIV are at heightened risk of developing Kaposi sarcoma (KS), non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, collectively termed as AIDS-defining cancers (ADCs) [2, 3]. With the advent of more effective combination antiretroviral therapy (cART) and the associated increases in survival, non-AIDS-defining cancers, including anal cancer, Hodgkin's lymphoma, hepatocellular carcinoma, renal carcinoma and lung cancer, have emerged as threats among HIV-infected people [4].

Similar to HIV, end-stage renal disease (ESRD) is a significant source of morbidity, with >700 000 dialysis patients in the USA [5]. Patients on dialysis also have an increased risk of malignancy [6, 7]. The associated uremic and pro-inflammatory states likely lead to alterations of the innate and adaptive immune systems, possibly providing a safe haven for malignancy development [7]. Among dialysis patients from 1996 to 2009, there was an increased risk of developing renal carcinoma, bladder carcinoma, breast cancer, NHL and colorectal cancer [6].

Although HIV and ESRD have clearly distinct pathophysiologies, connections between the two have been established. Kidney dysfunction is a common complication of HIV infection, attributable to both the adverse renal effects of commonly prescribed antiretroviral therapy as well as the direct nephrotoxic effects of the virus [8]. Moreover, ESRD is a potential late-stage complication of HIV infection usually secondary to HIV-associated nephropathy [9]. A previous analysis demonstrated ~1% of incident dialysis patients in the USA between 2005 and 2008 carried an HIV diagnosis [10]. Thus, there is a sizeable cohort of HIV-infected patients living on dialysis. We theorized that concurrent HIV infection and ESRD requiring dialysis may interact synergistically to potentiate the risk of malignancy. To address this question, we investigated the incidence and risk factors for specific malignancies among a large national cohort of HIV-infected dialysis patients. The results of this work may heighten awareness, and improve screening efforts and management strategies of common cancers within this at-risk group.

MATERIALS AND METHODS

Study sample and the US Renal Data System

All HIV-infected patients with an incident dialysis date between 2005 and 2011 were queried from the US Renal Data System (USRDS). The USRDS is a de-identified, national dataset that collects, analyzes and distributes information relevant to ESRD and dialysis. Available data include physician/supplier Medicare claims, vital statistics, treatments and outcomes on all ESRD patients in the USA. All study participants were aged ≥ 18 years. Patients with unknown age, sex, race, ethnicity or no follow-up were excluded.

Outcome variables

The primary outcome variables were select malignancy diagnoses, including NHL, KS, multiple myeloma, melanoma and Hodgkin's lymphoma. Additional malignancies by site included: colorectal, lung, kidney/renal pelvis, anal, liver, prostate,

bladder, breast, cervical, oral, pharyngeal, stomach, pancreas, laryngeal, thyroid and lip. These malignancies were investigated because they were previously found to be more common in either HIV-infected or dialysis patients. Subjects were defined as having any cancer if they had any one of the above diagnoses occurring after both the date of HIV diagnosis and the initiation of dialysis. International Classification of Diseases, Ninth Revision (ICD-9) codes from hospital claims data were used to define all diagnoses.

Independent variables

Demographic and clinical variables were determined using Centers for Medicare and Medicaid Services Medical Evidence Form 2728 and hospital claims data. Demographic variables included age at incident dialysis, race, gender and ethnicity. Access type and dialysis modality at the initiation of dialysis were included for descriptive purposes. Clinical diagnoses occurring before cancer diagnosis or last claim date were determined using ICD-9 codes from hospital claims data and included: tobacco or alcohol use, hepatitis B, hepatitis C, *Helicobacter pylori* infection, obesity, history of noncompliance, history of cancer, cystic kidney disease, prior transplant (kidney, heart, heart valve, bone, lung, liver, other specified organs and unspecified organ transplants, excluding skin and corneal transplants), inflammatory bowel disease, diabetes mellitus and liver cirrhosis. AIDS-defining opportunistic infections (ADOIs) were also determined using ICD-9 codes and must have occurred after the date of the first HIV diagnosis minus 30 days, and before the cancer date or last claim date. For ADOIs, the number of infections was classified as zero, one, or two or more of the following: esophageal candidiasis, coccidioidomycosis, cryptococcosis, cryptosporidiosis, cytomegalovirus, visceral herpes simplex, disseminated or extrapulmonary histoplasmosis, isosporiasis, disseminated or extrapulmonary *Mycobacterium avium* and other/unspecified *Mycobacterium* species infection, *Mycobacterium tuberculosis*, pneumocystosis, progressive multifocal leukoencephalopathy, *Salmonella* septicemia and toxoplasmosis of the brain.

Statistical analysis

All statistical analyses were performed using SAS version 9.4, and statistical significance was assessed at a level of 0.05. Descriptive statistics were determined for any cancer overall and for the three most common cancers. Chi-square tests and t-tests were used to examine preliminary differences between those with and without a cancer diagnosis.

To examine the relative risk (RR) of demographics and clinical diagnoses for any cancer and for each of the three most common cancers, generalized linear models were used assuming a binomial distribution and logit link, and an offset parameter of the natural log of the person-years contributed by each individual. Each potential independent risk factor was first examined in simple bivariate models and the RR and corresponding 95% confidence interval (CI) were estimated. All variables were then entered into a comprehensive full model, and a backward model building strategy was used to arrive at the final model. Variables that had the least significant P-value in the full model were eliminated one-by-one until the final model consisted of those variables that were statistically significant at the 0.05 alpha level or needed in the model based on the model fit criteria. A version of the quasi-likelihood under the independence model criterion (QICu) was examined after each

Table 1. Demographics of the HIV-infected dialysis patient cohort stratified by presence of a cancer diagnosis

Demographic	Overall (n = 6641)	Any cancer diagnosis (n = 543)	No cancer diagnosis (n = 6098)
Age at incident dialysis (mean ± SD), years	47.8 ± 11.5	49.7 ± 11.7*	47.6 ± 11.5
Sex, n (%)			
Female	2001 (30.1)	118 (21.7)*	1883 (30.9)
Male	4640 (69.9)	425 (78.3)*	4215 (69.1)
Race, n (%)			
Black	5313 (80.0)	413 (76.1)*	4900 (80.4)
White/other	1328 (20.0)	130 (23.9)*	1198 (19.7)
Ethnicity, n (%)			
Hispanic	486 (7.3)	39 (7.2)	447 (7.3)
Non-Hispanic	6155 (92.7)	504 (92.8)	5651 (92.7)
Dialysis modality, n (%)			
Hemodialysis	6322 (95.2)	522 (96.1)	5800 (95.1)
Peritoneal dialysis	247 (3.7)	18 (3.3)	229 (3.8)
Other/unknown	72 (1.1)	<11	69 (1.1)
Access type, n (%)			
Catheter	5342 (80.4)	424 (78.1)	4918 (80.7)
Graft	139 (2.1)	13 (2.4)	126 (2.1)
Arteriovenous fistula	519 (7.8)	48 (8.8)	471 (7.7)
Other/unknown	641 (9.7)	58 (10.7)	583 (9.6)
Years from dialysis to cancer diagnosis or last claim date (mean ± SD)	2.2 ± 1.7	1.5 ± 1.4*	2.2 ± 1.7

*P < 0.05 when compared with patients without a cancer diagnosis.

nonsignificant variable was removed from the model. The adjusted RR (aRR) and corresponding 95% CI were estimated for each variable; the aRR represents the RR for that specific variable adjusting for all other variables in the model.

RESULTS

Study population

A total of 6641 HIV-infected dialysis patients were identified. As seen in Table 1, the mean age of all patients was 48 ± 12 years. The cohort was 70% male and 80% black. There were 543 individuals (8.2%) diagnosed with any cancer. Patients with cancer were more likely to be older, male and white or other race when compared with those without a cancer diagnosis. Among those with a cancer diagnosis, the average time from start of dialysis to diagnosis was 1.5 years.

Cancer incidence

Overall, 603 cancer diagnoses were identified among 543 patients. There were 57 patients with more than one cancer (Table 2). The incidence of cancer over the entire study period was 8.2%. The annual incidence and a Kaplan–Meier curve of all cancers are shown in Figure 1. The top six malignancies included NHL (n = 135), KS (n = 86), colorectal carcinoma (n = 70), lung (n = 61), kidney and renal pelvis (n = 40) and anal (n = 37). Descriptive statistics for the three most common malignancies are in Table 3.

ADOIs

Within the cohort of 6641 HIV-infected dialysis patients, 833 (12.5%) developed at least one ADOI. A total of 1043 ADOI diagnoses were identified (Table 4) with some patients receiving more than one diagnosis. The most common ADOIs included *Pneumocystis jirovecii* pneumonia (n = 295), esophageal

Table 2. Incidence of malignancies in the HIV-infected dialysis patient cohort (n = 6641)

Malignancy	Frequency (%)
NHL	135 (24.9)
KS	86 (15.8)
Colorectal	70 (12.9)
Lung	61 (11.2)
Kidney/renal pelvis	40 (7.4)
Anal	37 (6.8)
Liver	32 (5.9)
Other	31 (5.7)
Prostate	28 (5.2)
Multiple myeloma	27 (5.0)
Hodgkin's lymphoma	24 (4.4)
Bladder	11 (2.0)
Breast	11 (2.0)
Cervical	<11
Total	603

Percentages calculated based on 543 individuals with any cancer diagnosis. Others include: oral, pharyngeal, stomach, pancreas, laryngeal, thyroid, lip and melanoma.

candidiasis (n = 268) and disseminated/extrapulmonary *M. avium* complex (MAC; n = 114).

Risk factors for cancer

Risk factors (aRR and 95% CI) for the diagnosis of any cancer, and the top three cancer diagnoses, are shown in Figure 2. Tables containing data from the crude and adjusted models are provided in the Supplementary data. Variables that increased the risk of any cancer diagnosis (Figure 2A) included history of cancer (aRR = 5.37), liver cirrhosis (aRR = 2.30), male sex (aRR = 1.54), hepatitis B (aRR = 1.52) and age (aRR = 1.03 for every

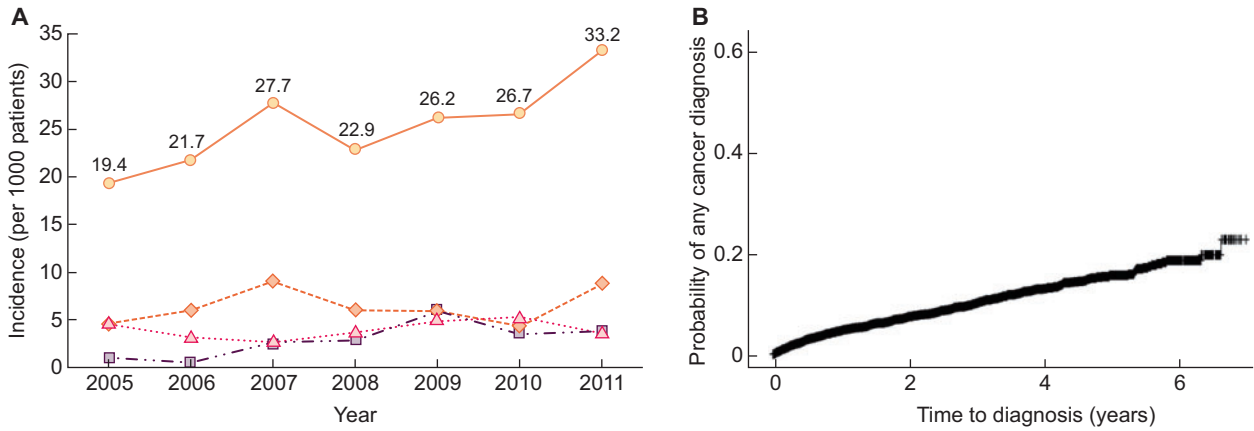


FIGURE 1: Incidence and occurrence of HIV related cancers in dialysis patients. (A) Annual incidence per 1000 patients from 2005 to 2011. Any cancer (solid line); NHL (heavy dashed line); KS (dotted line); and colorectal cancer (dashed and dotted line). The figure shows an overall increase in the incidence of all tumors. (B) Kaplan-Meier curve showing the probability occurrence of any cancer diagnosis over the same period.

1 year increase). With regard to ADOIs, having one or two or more ADOIs increased the risk of a cancer diagnosis (aRR = 2.23 and aRR = 3.11, respectively) when compared with no ADOI. Patients with hepatitis C were less likely to have a cancer diagnosis (aRR = 0.75).

Risk factors for the three most common cancers are shown in Figure 2B–D. For a diagnosis of NHL (Figure 2B), the highest RRs included history of cancer (aRR = 7.05), one ADOI (aRR = 2.52) or two or more ADOIs (aRR = 3.08), hepatitis B (aRR = 1.85) and male sex (aRR = 1.54). Hepatitis C was associated with a decreased risk (aRR = 0.48). The risk of KS (Figure 2C) was increased with male sex (aRR = 5.56), having one (aRR = 3.29) or two or more ADOIs (aRR = 6.78) and liver cirrhosis (aRR = 2.94). Increasing age (aRR = 0.98 for every 1 year increase) and black race (aRR = 0.55) were associated with a decreased risk. For colorectal cancer (Figure 2D), variables associated with an increased risk of diagnosis included history of cancer (aRR = 9.80), one ADOI (aRR = 2.67) or two or more ADOIs (aRR = 5.82), hepatitis B (aRR = 2.29), male sex (aRR = 1.96) and increasing age (aRR = 1.02 for every 1 year increase).

DISCUSSION

This is the first study investigating risk factors for malignancy in HIV-infected dialysis patients. We show that 8.2% of HIV-infected dialysis patients from 2005 to 2011 were diagnosed with at least one cancer, with NHL, KS and colorectal carcinoma being the most common diagnoses. A history of cancer and ADOIs were the most common risk factors for malignancy overall, conferring over 5.3- and 2.2-fold increases in risk, respectively.

We investigated patients at risk for cancer from both HIV and ESRD requiring dialysis. In the general population, the cumulative incidence of any malignancy from 2007 to 2011 was 0.48% [11]. This compares to a cumulative incidence of 4.8% in the overall HIV-infected population from 1996 to 2012 during the cART era [12]. Among dialysis patients from 1994 to 2014, the cumulative incidence of cancer was 3.5% [13]. Because the 8.2% incidence observed in our study appears to be greater than that previously reported for either patient with HIV or those receiving dialysis, we would theorize that the risks of cancer associated with each condition may be cumulative.

The most common malignancies identified in our cohort were NHL, KS and colorectal carcinoma. Our findings are similar

Table 3. Demographics of HIV-infected dialysis patients with the three most common malignancies

Demographic	NHL (n = 135)	KS (n = 86)	Colorectal Cancer (n = 70)
Age at incident dialysis (years) (mean ± SD)	46.2 ± 11.2	44.6 ± 9.8	49.5 ± 11.5
Sex, n (%)			
Female	30 (22.2)	<11	13 (18.6)
Male	105 (77.8)	80 (93.0)	57 (81.4)
Race, n (%)			
Black	105 (77.8)	60 (69.8)	49 (70.0)
White/other	30 (22.2)	26 (30.2)	21 (30.0)
Ethnicity, n (%)			
Hispanic	14 (10.4)	<11	<11
Non-Hispanic	121 (89.6)	79 (91.9)	67 (95.7)
Dialysis type, n (%)			
Hemodialysis	132 (97.8)	83 (96.5)	68 (97.1)
Peritoneal dialysis	<11	<11	<11
Other/unknown	<11	<11	<11
Access type, n (%)			
Catheter	107 (79.3)	64 (74.4)	56 (80.0)
Graft	<11	<11	<11
Arteriovenous fistula	<11	11 (12.8)	<11
Other/unknown	16 (11.9)	<11	<11
Years from dialysis to cancer diagnosis or last claim date (mean ± SD)	1.3 ± 1.2	1.3 ± 1.3	2.1 ± 1.7

to previous studies of cancer in HIV-infected individuals. Among 86 620 HIV-infected participants of the North American AIDS Cohort Collaboration on Research and Design trial from 1996 to 2009, the most common cancers were NHL, KS and lung cancer [14]. In 2010, the most common cancers diagnosed among HIV-infected patients in the USA were NHL, followed closely by KS, lung cancer and anal cancer [15]. When looking at dialysis patients, a study among Medicare patients from 1996 to 2009 identified prostate, lung and colorectal cancers as most common [6]. Another study of dialysis patients from Hong Kong found that colorectal, renal cell and lung cancers were most common [13]. Taken together, our data support these other studies and demonstrate that HIV-infected dialysis patients are susceptible to NHL and KS, but with the added risk of colorectal cancer as commonly seen in the general dialysis population.

Table 4. Distribution of ADOIs

OIs	Count (%)
<i>Pneumocystis jirovecii</i> pneumonia	295 (28.3)
Candidiasis (esophageal)	268 (25.7)
<i>Mycobacterium avium</i> (disseminated or extrapulmonary)	114 (10.9)
Cytomegalovirus	102 (9.8)
Cryptococcosis (extrapulmonary)	85 (8.1)
Toxoplasmosis of brain	49 (4.7)
<i>Mycobacterium tuberculosis</i>	40 (3.8)
Histoplasmosis (disseminated or extrapulmonary)	28 (2.7)
Progressive multifocal leukoencephalopathy	20 (1.9)
Cryptosporidiosis (chronic intestinal)	18 (1.7)
Herpes simplex (visceral)	17 (1.6)
Other	<11
Total	1043

Others include: coccidioidomycosis (disseminated or extrapulmonary), *Salmonella* septicemia, isosporiasis (chronic intestinal).

The fact that NHL and KS were the most frequently diagnosed cancers is notable given that our cohort was confined to incident dialysis patients from 2005 to 2011, an era when cART was widely available in the USA, whereas other studies of HIV-infected individuals have shown decreasing incidence of NHL and KS following initiation of cART [16–18]. All dialysis patients are insured through Medicare and thus should have access to cART. Whether this finding represents a heightened risk for these traditional ADCs due to additive immunomodulatory effects of HIV and ESRD, or perhaps a different pattern of cART utilization in HIV-infected dialysis patients, suggests a future area for investigation.

In our cohort, the most significant risk factor for the development of any cancer, as well as NHL and colorectal cancer individually, was a history of cancer. The increased risk for the development of a secondary cancer may be due to genetic or acquired susceptibility to malignancy, and/or be a surrogate marker for immune dysregulation that leads to impaired tumor surveillance. The risk for secondary cancers has previously been noted in HIV-infected patients with cancer. In one US cohort of HIV-infected patients with cancer, 7.4% were diagnosed with a second malignancy [17]. Among patients with KS, secondary malignancies developed at a 94% greater incidence than expected [19]. Our finding is consistent with these observations and may represent a true risk. Alternatively, the magnitude of the RR of previous cancer may have been artificially amplified by a coding artifact, whereby the diagnosis of history of cancer and the diagnosis of incident cancer on dialysis overlapped. We attempted to reduce the risk of coding artifact in this query by specifically defining the history of cancer as having been coded prior to the initial diagnosis date for the incident malignancy identified after the initiation of dialysis.

This study identified 1043 ADOIs in 833 (12.5%) HIV-infected dialysis patients. The most common were *P. jirovecii* pneumonia, esophageal candidiasis and disseminated/extrapulmonary MAC. This is consistent with previous data showing the same pattern and demonstrating that among 63 541 HIV patients, 9.2% developed at least one ADOI [20]. Although these two rates are not directly comparable, it does raise the question of whether the increased physiological stress of ESRD and dialysis in patients with HIV may lead to a heightened risk of opportunistic infections. Differences in cART utilization may also contribute to the observed difference, but because the USRDS does

not include patient-specific data in regards to medication utilization, this aspect was beyond the scope of this study.

Our data indicate that ADOIs were significant risk factors for the development of any malignancy. ADOIs characteristically infect patients with low CD4⁺ cell counts, and thus the presence of an ADOI represents a weakened immune system with decreased immune surveillance for malignancy [21]. The USRDS is an administrative dataset, thus we did not have access to specific CD4⁺ cell counts. However, prior studies of HIV-infected patients have shown a link between the incidence of noncancer AIDS events such as ADOIs and increased cancer risk [17].

In our study, demographic risk factors for cancer in HIV-infected dialysis patients included age and male sex. Similar to the general population, the risk of all cancers increases with age [22]. Age-related reductions in circulating naïve T cells and decreased CD4/CD8 ratios [23] may be further amplified in HIV patients. The increased malignancy risk among males with HIV and ESRD on dialysis closely mirrors the incidence and mortality of males in the general population [24–26].

Hepatitis B was a risk factor for cancer in our cohort. It is the leading cause of hepatocellular carcinoma worldwide, and both dialysis patients and HIV-infected individuals have an increased risk of chronic hepatitis B infection [27, 28]. Additionally, chronic hepatitis B has been described as a predictor of ADCs in HIV-infected patients [29, 30]. Once infected, the virus can be detected in a wide range of extrahepatic tissues including blood mononuclear cells, lymph nodes, spleen and brain [31]. We speculate that HIV-infected dialysis patients, through immune dysregulation, may have heightened susceptibility to the oncogenic effects of chronic infection with hepatitis B.

Similar to previous studies, there was a decreased risk of KS with black race in our cohort, possibly due to underlying genetic differences and/or under-diagnosis secondary to darker skin [19, 32, 33]. In addition, hepatitis C infection was associated with decreased risk for malignancy overall and NHL specifically. The explanation for this effect is unclear, but we theorize that morbidity associated with hepatitis C [34] may lead to earlier mortality and thus less time for cancer development.

This study has several limitations. First, from the USRDS dataset, clinical disease is inferred by ICD-9 diagnosis codes. The dataset does not include specific clinical results (such as laboratory data, biopsy results or culture data); thus, the existence of each comorbidity cannot be validated using clinical data. However, the accuracy of ICD-9 coding for HIV, cancer and some opportunistic infections has been validated in the general population [35, 36]. Moreover and when available, we used more than one code to identify a comorbidity, further conferring accuracy to an inferred diagnosis [35]. Second, we did not include squamous cell and basal cell skin cancers. The tumors were excluded primarily because they tend to be outpatient diseases and thus not captured in the inpatient hospital codes. This underestimation of overall malignancy incidence is a limitation of the study. Third, we did not have access to the use of antiretroviral therapy, which may have influenced malignancy incidence and represents an interesting avenue for future investigation. Finally, it is not possible to account for misdiagnoses or inaccurate coding. These limitations are partially balanced by large number of patients included in the analysis. In this regard, the USRDS dataset represents a comprehensive national cohort of Medicare-funded ESRD patients in the USA.

Despite the above limitations, the results of our study have several potential clinical implications. First, the index of clinical suspicion for malignancy should be increased in any HIV-

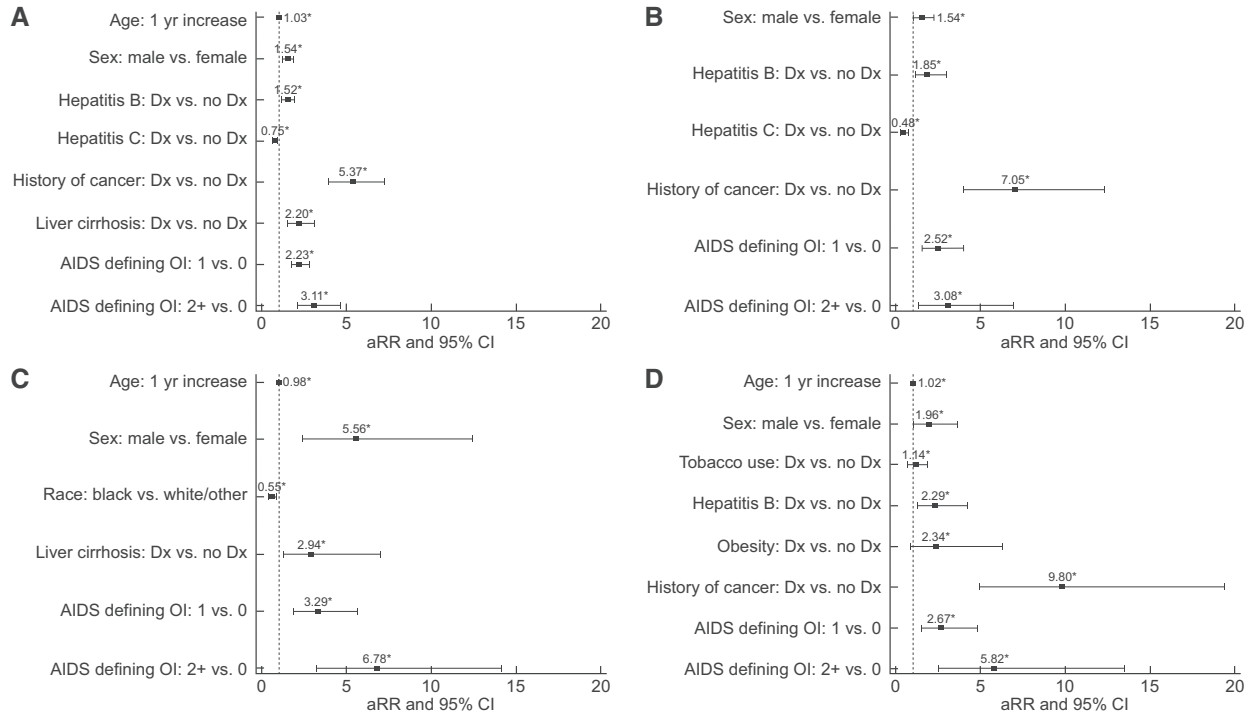


FIGURE 2: Risk factors for the diagnosis of any cancer overall (A), NHL (B), KS (C) and colorectal cancer (D). The vertical dashed line represents an aRR of 1.0 indicating no increased or decreased risk of diagnosis. *P < 0.05. Dx, diagnosis.

infected dialysis patient with a history of cancer or an ADOI. Second, providers should be aware of the increased risk of colorectal cancer in the HIV-infected dialysis patient and follow appropriate screening and diagnostic colonoscopy practices. Third, awareness of risk factors for malignancy in the HIV-infected dialysis patient should become part of routine dialysis provider visits with the intent of earlier diagnosis and therapy. Finally, preventive measures including adherence to viral vaccinations, compliance with cART therapy and regular surveillance by an experienced HIV physician should be implemented.

In conclusion, 8.2% of HIV-infected dialysis patients were diagnosed with a malignancy. The three most common cancers were NHL, KS and colorectal cancer. Major risk factors for the development of cancer include a history of cancer and development of ADOIs. Care providers for HIV-infected dialysis patients should be vigilant about assessing risk factors and warning signs for cancer and encourage compliance with all preventive screening tools and cART therapy.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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The data reported were supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government. The contents do not represent the views of the Department of Veterans Affairs or the US government.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the design of the study and the preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

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