Survival outcomes of primary cutaneous T-cell lymphoma in HIV-infected patients: a national population-based study

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ABSTRACT

This study aimed to investigate clinical characteristics and survival outcomes of primary cutaneous T-cell lymphoma (CTCL) in HIV-infected and non-HIV-infected patients. All data were from the Surveillance, Epidemiology, and End Results program, 1973–2013, of the U.S. National Cancer Institute. Data of 318 HIV-infected patients and 1272 non-HIV-infected patients with primary CTCL were analyzed. Endpoints were overall survival and cancer-specific mortality. Independent variables included demographics, pre-existing malignancy, treatments, and environmental factors. Among 8823 patients with CTCL, 318 (3.60 per cent) were HIV-infected and 8505 (96.40 per cent) were not. 318 HIV-infected patients and 1272 non-HIV-infected patients selected by matching diagnosis dates were analyzed, including 941 (59.2 per cent) males and 649 (40.8 per cent) females with mean age 58.8 years. HIV-infected patients with CTCL had higher survival and significantly lower risk of overall mortality than non-HIV-infected patients (adjusted HR 0.37, 95 per cent CI 0.24 to 0.59, P<0.001). Non-HIV-infected, age and black race were significant risk factors for overall mortality. Age and race are independent risk factors for overall mortality in primary CTCL individuals, and HIV-infected status is an independent protective factor, suggesting that advanced antiretroviral therapy restores immunity and prolongs survival in HIV-infected patients with CTCL.

Significance of this study

What is already known about this subject?

- Cutaneous T-cell lymphoma (CTCL) does occur in HIV-infected patients, sometimes with mixed-subtype diagnoses.
- It was described two HIV-infected patients with disease that resembled mycosis fungoides, but with Sézary-like cells in the dermis and epidermis.
- Because primary CTCL is rare among HIV-infected patients, few recent discussions or population-based studies have focused on the relationship between cutaneous disease in patients with HIV/AIDS.

What are the new findings?

- The survival rate in HIV-infected patients with CTCL was higher than that in non-HIV-infected patients.
- The risk of overall mortality was significantly lower in HIV-infected patients than in non-HIV-infected patients.
- The risk of overall mortality increased significantly with age and black race.
- The survival time of patients with primary CTCL was significantly longer in HIV-infected patients than in non-HIV-infected patients.

How might these results change the focus of research or clinical practice?

- In light of the results from the present study, healthcare providers can provide a different expectation in this specific HIV-infected group, especially if patients were under control of immunosuppression state.

INTRODUCTION

HIV infection is associated with an elevated risk for malignancies.[1 2] During the AIDS epidemic, these malignancies resulted in significant morbidity and mortality among HIV-infected individuals and accounted for a significant number of HIV-related and AIDS-related deaths.[2 3] Malignancies commonly associated with AIDS include Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and invasive cervical carcinoma.[4] However, while cancer rates have increased in HIV-infected patients for some cancers (eg, liver, prostate, and anal cancer), rates have declined for KS, NHL, and Hodgkin's lymphoma.[4] Even after the introduction of antiretroviral therapy (ART) and noted decreases in the incidence of KS and other HIV-associated malignancies,[5] cancer diagnoses are still made in >40 per cent of HIV-infected patients during the course of HIV infection, and >28 per cent of HIV-related deaths are

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still attributed to malignancy.[6–8] HIV-associated NHL is diagnosed most often in patients with advanced HIV, low CD4 count (<100 cells/μL), high HIV viral load, and prior AIDS diagnosis.[8–11] NHL is the most common and most frequently fatal among AIDS-defining illnesses,[12] although widespread administration of ART has improved survival rates dramatically.[13]

Mycosis fungoides is a common subtype of primary cutaneous T-cell lymphoma (CTCL) expressed as extranodal indolent NHL of T-cell origin with skin involvement; although it is an uncommon disease, it accounts for approximately 4 per cent of NHL cases.[12 13] CTCL does occur in HIV-infected patients, sometimes with mixed-subtype diagnoses. Zucker-Franklin *et al*[14] described two HIV-infected patients with disease that resembled mycosis fungoides, but with Sézary-like cells in the dermis and epidermis. Although the cutaneous disease can be disabling in patients with AIDS, such patients with low CD4 counts would not be expected to develop mycosis fungoides or CTCL because both neoplasms consist of helper T lymphocytes.[15] CTCL describes T-cell lymphomas that present primarily in the skin without evidence of extracutaneous disease at diagnosis. The most common forms of CTCL, including classic CTCLs (ie, mycosis fungoides, and its variants, including Sézary's syndrome) and primary cutaneous $CD30^+$ lymphoproliferative disorders (ie, anaplastic large-cell lymphoma and lymphomatoid papulosis), account for about 90 per cent of CTCLs in the Western world.[15] A study that examined changes in the epidemiological, immunological, pathological, or clinical characteristics of AIDS-related lymphoma found that even though ART and chemotherapy changed the course of the disease after the AIDS epidemic, the median survival of lymphoma patients had not changed as of 2000.[16] The relationship between cutaneous disease in patients with HIV/AIDS was described in the findings of earlier studies.[17–20] However, because primary CTCL is rare among HIV-infected patients, few recent discussions or population-based studies have focused on this topic. We hypothesized that analyzing risk factors and prognostic factors for primary CTCL in a large database of HIV-infected and non-HIV-infected groups might reveal the overall risk of mortality and the influence of demographic and clinical characteristics such as age, gender, race/ethnicity, residence status, environmental factors, and treatments received on survival. Therefore, this study aimed to investigate the unique clinical characteristics and survival outcomes of primary CTCL in HIV-infected and non-HIV-infected patients.

PATIENTS AND METHODS

Data source

All data for the present study were from the Surveillance, Epidemiology, and End Results (SEER), 1973–2013, of the National Cancer Institute Surveillance Research Program, Surveillance Systems Branch.[21] SEER was a nationally representative longitudinal survey conducted in the USA, and statistical data were made available to other researchers in April 2016. We received permission from the National Cancer Institute, USA, to use SEER data for research purposes (ref. # 10708, November 2016). All SEER data are deidentified, and data analysis for research purposes does not require IRB approval or informed consent by participating subjects.

Study population

The data of patients diagnosed with primary CTCL between January 1, 2004, and December 31, 2013, were extracted from the SEER-18 registry. Patients with missing data for age, gender, race/ethnicity, diagnosis year, and HIV status were excluded.

A total of 8823 patients diagnosed with primary CTCL defined according to the International Classification of Oncology Diseases, Third Revision (ICD-O-3) morphological codes (ICD-O-3: 9700–9709/3, 9718–9719/3, 9726–3), were identified in the SEER database between 2004 and 2013. Among these patients, 318 (3.60 per cent) were HIV-infected and 8505 (96.40 per cent) were non-HIV-infected. Numbers of HIV-infected patients in the SEER database increased significantly after year 2009. Therefore, to improve comparability between the two groups, non-HIV-infected patients were selected by matching diagnosis years of HIV-infected patients by a ratio of 4 to 1. The final analytic sample included 318 HIV-infected patients and 1272 non-HIV-infected patients with primary CTCL.

Outcome measures

The main endpoints of the present study were overall survival (OS) and cancer-specific mortality. OS was calculated from the day of diagnosis to the date of death from any cause. Cancer-specific mortality was defined as death from cancer calculated from the day of diagnosis to the date of death, indicated in the SEER database as 'vital status'. Independent variables evaluated for each case included patient demographics (age at diagnosis, sex, race/ethnicity, marital status), pre-existing malignancy, treatment performed (surgery, radiotherapy, or both), and environmental factors.

Statistical analysis

Continuous variables are presented as means±SD, and categorical data are shown as count and percentage. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify potential risk factors for overall mortality and cancer-specific mortality. Kaplan-Meier curves with log-rank test were used to evaluate OS and cancer-specific survival between patients with HIV and non-HIV patients. Statistical significance was set at <0.05. All statistical analyses were performed by SAS statistical software V.9.4 (SAS) and R software (R Foundation for Statistical Computing, Vienna, Austria).[22]

RESULTS

A total of 8823 patients with CTCL were identified in the SEER database from 2004 to 2013, including 318 (3.60 per cent) HIV-infected patients and 8505 (96.40 per cent) non-HIV-infected patients. To improve comparability, non-HIV-infected patients were selected by matching diagnosis years of HIV-infected patients by a 4:1 ratio, and the final analytic sample included 1590 patients with primary CTCL, consisting of 318 HIV-infected patients and 1272 non-HIV-infected patients.

Table 1 Basic characteristics of study population in patients with cutaneous T-cell lymphoma

Variables	Total (n=1590) n (%)	Non-HIV (n=1272) n (%)	HIV (n=318) n (%)
Age	58.8±18.1	59.1±18.2	57.5±17.7
Gender			
Male	941 (59.2)	749 (58.9)	192 (60.4)
Female	649 (40.8)	523 (41.1)	126 (39.6)
Race/ethnicity			
White	1162 (73.1)	925 (72.7)	237 (74.5)
Black	203 (12.8)	151 (11.9)	52 (16.4)
Asian or Pacific Islander	113 (7.1)	92 (7.2)	21 (6.6)
Others*	112 (7.0)	104 (8.2)	8 (2.5)
Marital status at diagnosis			
Single†	527 (33.1)	425 (33.4)	102 (32.1)
Married	748 (47.0)	582 (45.8)	166 (52.2)
Unknown	315 (19.8)	265 (20.8)	50 (15.7)
Region of SEER registry			
West	1010 (63.5)	811 (63.8)	199 (62.6)
South	217 (13.7)	180 (14.2)	37 (11.6)
North Central	219 (13.8)	196 (15.3)	23 (7.2)
Northeast	144 (9.0)	85 (6.7)	59 (18.6)
Previous primary malignancy			
No	1313 (82.6)	1050 (82.6)	263 (82.7)
Yes	277 (17.4)	222 (17.5)	55 (17.3)
Treatment			
No treatment‡	956 (60.1)	743 (58.4)	213 (67.0)
With treatment§	318 (20.0)	281 (22.1)	37 (11.6)
Not applicable/unknown/ missing	316 (19.9)	248 (19.5)	68 (21.4)

*Including American Indian, Alaska Native, other unspecified, and unknown.
†Including single, separated, divorced, and widowed.
‡Including no surgery or no radiotherapy as provided by the SEER database. Other modality of treatment was unknown.
§Including surgery or radiotherapy.
SEER, Surveillance, Epidemiology, and End Results.

Demographic and clinical characteristics of study subjects

Table 1 lists the demographic and clinical characteristics of the 1590 patients with primary CTCL in HIV and non-HIV groups. Mean age was 58.8 years, with 941 (59.2 per cent) males and 649 (40.8 per cent) females. A majority of patients were of white race (73.1 per cent), married (47.0 per cent), with no previous primary malignancy (82.6 per cent). Among all patients, 20.0% of patients with primary CTCL had undergone surgery or radiotherapy, and up to 60.1 per cent of patients had not received surgery or radiotherapy. No other detailed modalities were listed in the database (table 1).

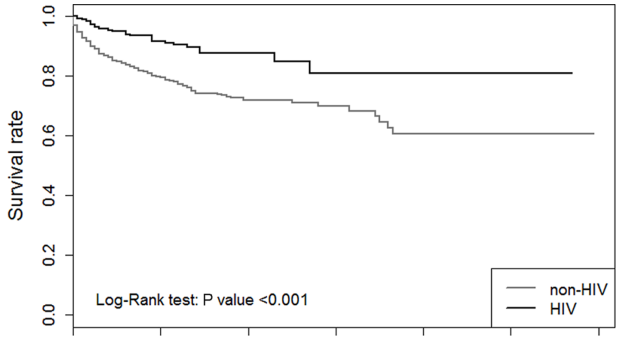

Figure 1 Kaplan-Meier curve of HIV and non-HIV-infected groups for overall survival.

Survival time by group

During the study period, 153 clinical events occurred overall due to primary CTCL, and a total of 274 patients died. Median survival was 14 months (IQR 5–28 months). Among non-HIV-infected patients, 140 events occurred due to primary CTCL and a total of 247 patients died. Median survival was 14 months (IQR 4–27 months). Among HIV-infected patients, 13 events occurred due to primary CTCL and a total of 27 (8.5 per cent) patients died. Median survival was 17 months (IQR 8–31 months) (data not shown).

Risk factors for mortality by group

The Kaplan-Meier survival curve showed that the survival rate in HIV-infected patients was higher than that in non-HIV-infected patients (figure 1). Results of univariate and multivariate Cox proportional hazard regression analyses are shown in table 2. Risk of overall mortality was significantly decreased in HIV-infected patients compared with that in non-HIV-infected patients (adjusted HR (aHR) 0.37, 95 per cent CI 0.24 to 0.59, P<0.001). Non-HIV-infected status, age, and race were significant risk factors for overall mortality. In the multivariate model, the risk of overall mortality increased significantly with age (aHR 1.04, 95 per cent CI 1.03 to 1.05, P<0.001) and black race (aHR 1.57, 95 per cent CI 1.05 to 2.34, P=0.029) compared with age and racial counterparts.

For cancer-specific mortality, the survival rate of patients with primary CTCL was significantly higher in HIV-infected patients than in non-HIV-infected patients (P<0.001) (figure 2). HIV-infected status and living in the North Central region of the USA were associated with decreased cancer-specific mortality (aHR 0.29, 95 per cent CI 0.15 to 0.56, P<0.001; aHR 0.50, 95 per cent CI 0.26 to 0.94, P=0.033), while age (aHR 1.02, 95 per cent CI 1.01 to 1.03, P<0.001) was still a significant risk factor for primary CTCL mortality (figure 2, table 2).

DISCUSSION

Results of the present study revealed that the survival rate in HIV-infected patients with CTCL was higher than that in non-HIV-infected patients. The median survival among all patients with primary CTCL was 14 months and was also 14 months in non-HIV-infected patients. In HIV-infected patients, the median survival was 17 months. The risk factors for mortality were also different. The risk of overall mortality was significantly lower in HIV-infected patients than in non-HIV-infected patients, and the risk of overall mortality increased significantly with age and black race. Analysis of cancer-specific mortality showed that the survival time of patients with primary CTCL was significantly longer in HIV-infected patients than in non-HIV-infected patients. HIV status and residence region (ie, living

Table 2 Univariate and multivariate Cox hazard regression for risk of overall mortality and cancer-specific mortality in primary cutaneous T-cell lymphoma

	Overall mortality				Cancer-specific mortality			
Variable	**HR (95% CI)**	**P value**	**aHR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**aHR (95% CI)**	**P value**
Case								
Non-HIV	Reference		Reference		Reference		Reference	
HIV	**0.39 (0.27 to 0.58)**	**<0.001**	**0.37 (0.24 to 0.59)**	**<0.001**	**0.33 (0.19 to 0.58)**	**<0.001**	**0.29 (0.15 to 0.56)**	**<0.001**
Age	**1.04 (1.03 to 1.05)**	**<0.001**	**1.04 (1.03 to 1.05)**	**<0.001**	**1.02 (1.01 to 1.03)**	**<0.001**	**1.02 (1.01 to 1.03)**	**<0.001**
Gender								
Male	Reference		Reference		Reference		Reference	
Female	0.84 (0.66 to 1.07)	0.148	0.85 (0.64 to 1.12)	0.247	0.95 (0.69 to 1.31)	0.763	0.94 (0.65 to 1.37)	0.752
Race/ethnicity								
White	Reference		Reference		Reference		Reference	
Black	0.99 (0.70 to 1.42)	0.966	**1.57 (1.05 to 2.34)**	**0.029**	0.82 (0.49 to 1.36)	0.442	1.39 (0.80 to 2.41)	0.249
Asian or Pacific Islander	1.1 (0.69 to 1.75)	0.687	1.37 (0.76 to 2.47)	0.292	1.47 (0.85 to 2.54)	0.164	1.42 (0.72 to 2.79)	0.314
Others*	**0.37 (0.17 to 0.82)**	**0.015**	0.46 (0.11 to 1.97)	0.296	0.36 (0.12 to 1.08)	0.532	0.33 (0.05 to 2.39)	0.271
Marital status at diagnosis								
Single†	Reference		Reference		Reference		Reference	
Married	0.85 (0.67 to 1.09)	0.195	0.85 (0.65 to 1.13)	0.267	0.92 (0.66 to 1.28)	0.620	0.92 (0.63 to 1.33)	0.654
Region of SEER registry								
West	Reference		Reference		Reference		Reference	
South	1.16 (0.80 to 1.66)	0.436	0.96 (0.63 to 1.46)	0.844	0.91 (0.54 to 1.51)	0.701	0.79 (0.43 to 1.47)	0.454
North Central	0.86 (0.61 to 1.22)	0.403	0.70 (0.48 to 1.03)	0.072	**0.50 (0.28 to 0.89)**	**0.018**	**0.50 (0.26 to 0.94)**	**0.033**
Northeast	0.76 (0.46 to 1.24)	0.267	1.13 (0.69 to 1.85)	0.642	0.88 (0.49 to 1.58)	0.670	1.21 (0.66 to 2.21)	0.537
Treatments								
No treatment‡	Reference		Reference		Reference		Reference	
With treatment§	1.24 (0.94 to 1.64)	0.126	0.99 (0.75 to 1.34)	0.995	1.06 (0.72 to 1.57)	0.762	0.88 (0.58 to 1.30)	0.499

Bold text indicates a statistically significant difference with P<0.05.
*Including American Indian, Alaska Native, other unspecified, and unknown.
†Including single, separated, divorced, and widowed.
‡Including no surgery or no radiotherapy as provided by the SEER database. Other modality of treatment was unknown.
§Including surgery or radiotherapy.
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in the North Central region of the USA) were associated with lower cancer-specific mortality.

The evaluation of primary CTCL among HIV-infected and non-HIV subjects in the present study revealed that the mean age of HIV-infected patients (57.5) was somewhat younger than that of non-HIV patients (59.1 years), although not significantly so. Although CTCL and its subtypes can occur at any age, the peak age at presentation of mycosis fungoides is 55–60 years and older.[11] Advanced age is the greatest risk factor for AIDS-defining cancers.[23] While older age was significantly associated with increased risk of overall mortality, HIV-infected status was significantly associated with decreased risk of overall mortality and was an independent protective factor for cancer-specific mortality.

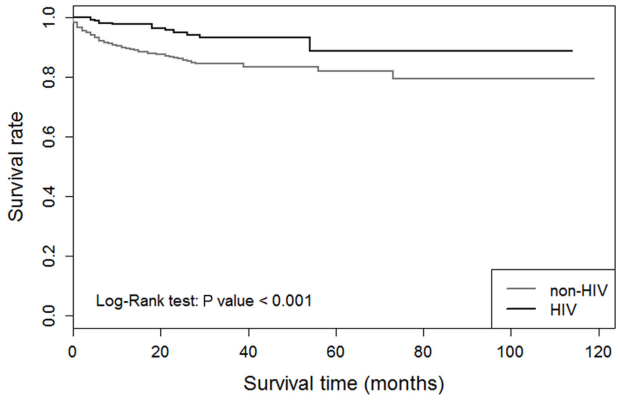

Figure 2 Kaplan-Meier curve of HIV and non-HIV-infected group for cancer-specific survival.

In the present study, black race was also significantly associated with increased risk of overall mortality. At the same time, males and white race were predominant among HIV-infected patients with CTCL. In contrast, mycosis fungoides is reported to be more common in males and blacks.[11] Although the predominant race among HIV-infected individuals in the USA is African-American,[24] the study population in the present study comprised individuals with primary CTCL who tested HIV-positive; hence, the racial distribution may be different from that documented under HIV diagnosis in the SEER data. Also, data from the SEER database showed that, among all individuals with NHL, only those with primary CTCL had undergone HIV testing, indicating that perhaps other malignancies in HIV-positive individuals could have been of black or other racial origins. The 2015 Surveillance Report of the Centers for Disease Control and Prevention (CDC)[24] states that African-Americans continue to experience the greatest burden

of HIV compared with other races and ethnicities, representing 12 per cent of the US population, but accounting for 45 per cent (17,670) of HIV diagnoses.

Among all subjects in the present study, 20.0 per cent of those with primary CTCL had undergone surgery or radiotherapy, and up to 60.1 per cent had not received either of these treatments. In other studies, surgical excision or radiotherapy was reported to be the curative measure for rare subtypes of CTCL, and surgical excision or radiotherapy usually results in complete remission of mycosis fungoides, although relapses may occur.[25]

Results of the present study showed that risk of overall mortality was significantly lower in HIV-infected patients with primary CTCL than in non-HIV-infected patients, as well as the risk of cancer-specific mortality. These results strongly suggest the protective effects of HIV-infected status. However, since the SEER data only included the treatment modalities like radiotherapy and surgical resection, use of ART to restore immune status and/or to treat CTCL cannot be confirmed. To clarify possible mechanisms is of interest and worthy of further investigation. Nevertheless, the literature presents substantial evidence to support our results. The overall incidence of specific AIDS-defining malignancies declined markedly after the introduction and widespread use of Highly Active Antiretroviral Therapy (HAART).[13] In HIV-positive individuals, HAART is reported to be an independent prognostic factor for OS, and its demonstrated induction of immunological restoration would have a significant impact on patient survival.[26] HAART produces both an immunological response that normalizes CD4 lymphocyte counts and a virological response that almost completely suppresses HIV viral replication (direct disease treatment), achieving at least partial immune restoration and decreasing the incidence of opportunistic infections, reducing the risk of developing NHL or KS, and prolonging the survival.[12 27]

Although the majority of HIV-infected patients in the present study had no previous malignancies, it is well known in clinical practice that HIV-infected individuals have an increased propensity for developing malignancy.[1–3] The incidence of Hodgkin's lymphoma, for example, is five- to ten-fold higher in HIV-infected individuals.[28] Additionally, a substantial portion of lymphocyte-depleted and mixed-cellularity Hodgkin's lymphoma cases are found in HIV-infected middle-aged men and Hispanic and non-Hispanic blacks.[29] HIV-infected patients have a possible 100-fold risk of developing NHL, often presenting with extranodal manifestations.[30] Early in the AIDS epidemic, an extremely high number of cases of KS were observed and, at that time, patients commonly received an especially aggressive clinical course.[31] In addition to such evidence, immunosuppression or HIV itself may play a role in oncogenesis as HIV-infected patients develop anti-HIV cytotoxic CD8+ lymphoproliferation.[32]

Other data suggest that malignancies such as KS or lymphoma may occur soon after the initiation of ART, arguing that the treatment itself rather than the increased life expectancy it confers may predispose towards these cancers.[33] However, when the timing of the development of malignancy relative to initiation of ART was studied in a cohort of 11,485 patients, 457 cancers developed within 10 years after ART was begun, including a higher incidence of KS and lymphomas in the first six months after ART initiation; results of that study showed that the incidence of KS and NHL correlated inversely with the CD4 cell count.[34] Increased incidence was attributed to the presence of more severe immunosuppression at the start of treatment, and possibly to unmasking subclinical NHL related to immune reconstitution inflammatory syndrome, but incidence eventually decreased in that population. Also, in that study, other cancers were noted to increase as time increased for ART administration, possibly reflecting increased cancer risk associated with aging. The authors recommended earlier HIV diagnosis and prompt ART initiation as well as ongoing aggressive cancer screening and prevention during HIV care.

It is worth mentioning, though not especially relevant to observations of overall mortality and cancer-specific mortality in the present study, that residing in the North Central region of the USA (SEER registries of metropolitan Detroit, Michigan, and in Iowa) was an independent protective factor for mortality. This is corroborated by the CDC HIV Surveillance Report for 2015,[20] which showed that the Midwest US had the fewest diagnoses of HIV infection in 2015, and only 11 per cent of deaths attributed directly to HIV or AIDS occurred in the midwest compared with the south 53 per cent, northeast 19 per cent, and west 17 per cent. The said SEER registries in the North Central region were overlapping with the states in the Midwest US.

Strengths and limitations

Results of the present study may be somewhat limited because data were analyzed retrospectively, limiting attribution of results to causation. Also, only a first course of therapy was included for patients with CTCL and the use of other treatment modalities and their impact on survival remained unknown, which could limit interpretation. In addition, the SEER database did not provide data on CD4 counts and ART for HIV-infected patients; therefore, effects of all possible treatment could not be compared between non-HIV and HIV-infected subjects in the present study, which we feel may be an important factor affecting survival in this population. However, the longitudinal analysis does allow inferences to causality to be made. This study was conducted using a nationally representative sample from the USA, minimizing discrepancies and biases and allowing results to be generalized to the US adult population. The large multiethnic population in the sample allowed exploration of heterogeneity in association with primary CTCL.

CONCLUSIONS

In individuals with CTCL, age is an independent risk factor for cancer-specific mortality and HIV-infected status is an independent protective factor. The survival rate in HIV-infected patients with CTCL is higher than that in non-HIV-infected patients. In light of results of the present study, the expectations of healthcare providers regarding outcomes of HIV-infected patients with CTCL may be more optimistic, especially if patients were being managed with ART promptly. Further prospective study of multiracial HIV-infected versus non-HIV patients with CTCL, together with their detailed treatments, is needed to corroborate our results.

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